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OF THE MEDICAL SCIENCES

MARCH, 1928

ORIGINAL ARTICLES.

A FAMILIAL HEMORRHAGIC CONDITION ASSOCIATED WITH PROLONGATION OF THE BLEEDING TIME.

By George R. Minot, M.D.,

BOSTON.

(From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.)

Atypical chronic cases of hemorrhagic diathesis are known to occur, and as more such examples are reported after studies by modern methods they should be better understood and classified. There exists apparently a chronic familial hemorrhagic condition distinct from recognized types of such disorders. Unlike hemophilia, it may occur in father and son, and it is not associated with prolongation of the coagulation time of the blood. In contrast to thrombopenic purpura (purpura hemorrhagica), the blood platelets are not decreased and the clot retracts normally. The condition is, however, characterized by marked prolongation of the bleeding time, which may be intermittently demonstrable. Five cases of this syndrome have been observed in members of two families and form the basis for this report.

The bleeding time is the time of duration of a hemorrhage which follows puncture of an ear lobe with a sharp needle. The blood is wiped up on blotting paper at regular intervals of from one to two minutes. Such a hemorrhage ceases normally in less than four minutes, and the drops diminish rapidly in size. Distinction between a bleeding time of one half hour and one three times as long can cause errors of judgment, because, when the bleeding time is grossly abnormal, the duration of hemorrhage from different punctures at about the same time may be of various lengths. Pro-

longation of the bleeding time is particularly associated with reduction of the blood platelets below about 100,000 per c.mm.; and when there occur only a few thousand per cubic millimeter, the bleeding lasts often for more than an hour. Thus, when the bleeding time is considerably prolonged, the patient usually will be found to suffer from one of the various types of thrombopenic purpura. Slight lengthening of the bleeding time—less than twelve minutes—may occur with diminution of fibrinogen; and in certain cases with dilated peripheral bloodvessels and anemia, but with an ample number of blood platelets. Temporary prolongation of the bleeding time has been observed to occur in some newborn infants without decreases of blood platelets.

When an individual experiences recurrently for years symptoms and signs of pathologic blood loss, and if his blood shows alteration in factors associated with clotting, the diagnosis is very probably hemophilia or chronic thrombopenic (thrombocytopenic) purpura. Hemophilia is an hereditary disease occurring in males, but transmitted by the female. In this disease the coagulation time of the blood is prolonged, usually markedly, and is associated with qualitatively defective blood platelets that occur in normal or increased numbers. The bleeding time is normal provided too large a puncture wound is not made. Chronic thrombopenic purpura is rarely familial. In this condition the blood platelets are much reduced in numbers and the bleeding time often greatly prolonged, but the blood clots in approximately normal time. The clot does not retract, which is in contrast to the hemophilic clot that does so normally. These two diseases are to be distinguished from chronic conditions in which hemorrhage is a symptom without abnormality of the factors associated with coagulation of the blood or prolongation of the bleeding time. For example: Idiopathic purpura with visceral or arthritic manifestations, hereditary telangiectasia, and the condition of "easy bruising" seen especially in women.

The chronic familial hemorrhagic condition associated with prolongation of the bleeding time and distinct from recognized types of such disorders is illustrated by the five cases cited below.

The first individual seen with this hemorrhagic syndrome is now a healthy appearing man, thirty-three years of age and of Anglo-Saxon descent. He has been studied numerous times during the past twelve years and has been mentioned formerly by Minot and Lee.[1] It has been stated that his paternal great-grandfather and grandfather, experienced many recurrent attacks of epistaxis. His father bled during his life in the same way as the patient, and died at the age of about fifty years from the results of a duodenal ulcer. He experienced, as did his son, more bleeding in youth than later in life. The father had three brothers and two sisters. None of these five persons is known to have bled abnormally except as indicated below. One brother had "violent nosebleeds" as a boy. Another

brother had two daughters, one of whom married. This woman had a daughter who died "two days after birth of bleeding through the skin." A sister of this child has shown on signs of a hemorrhagic diathesis. One of the father's two sisters, who died at the age of twenty-two years, may have suffered from a hemorrhagic syndrome.

The patient had one brother. He died at the age of twenty-two years of diabetes mellitus, but he never showed any tendency to bleeding. There are three sisters, the oldest of whom had violent nosebleeds as a child, but in spite of surgical operations she has had no other blood loss that might be due to an unusual cause. This sister has two sons and two daughters. The boys have had "nosebleeds very easily" and one has probably had small ecchymoses following trivial trauma. The girls have shown no signs to suggest abnormal bleeding. The patient's two other sisters have had no symptoms to suggest a hemorrhagic diathesis, but it is reported that prior to tonsillectomy, the bleeding time of one of them was abnormally long. However, no abnormal blood loss occurred from the operation.

The patient from the age of a few days to twelve years had recurrent frequent and often severe epistaxis. As a child he was "anemic" and had "serious digestive disturbances." At the age of seventeen years he bled for two weeks from a slight injury to his lip. At twenty-one years of age, he suffered from a nasal hemorrhage persisting for twelve days that caused a moderate degree of anemia. While the blood loss continued his blood clotted in normal time, but tended to exhibit a reclotting phenomenon. The antithrombin was slightly increased. The number of blood platelets was increased above normal. The bleeding time was between thirty and forty-five minutes. A few days after the epistaxis ceased the bleeding time was normal. A year later he had considerable bleeding from the gums over a period of days. In the following three years he occasionally developed an ecchymosis from less trauma than would probably produce a hemorrhage in a normal person. During these three years he had on two successive days a bleeding time of about an hour's duration, but tests at other times revealed it to be normal.

Seven years ago he was operated upon for acute appendicitis without hemorrhage at the time; but ten days later, bleeding from the wound occurred, probably dependent upon a local cause.

The patient has had many upper respiratory infections and attacks of tonsillitis, usually accompanied by nosebleeds. Three years ago the infected tonsils were cauterized, and at this time he had his last pronounced nosebleed. Since then, the patient has had no attack of tonsillitis and only a few "colds." In recent years no ecchymoses have developed without an adequate cause. The bleeding time has remained ten minutes or less and usually has been normal. At no time have the blood platelets been reduced or the blood coagulation time or clot retraction been abnormal. Physical and labora-

tory examinations have shown no other abnormalities than those referred to.

This man has three children, a son and two daughters. The mother and members of her family have had no symptoms to indicate any sort of hemorrhagic disorder, nor have the two daughters. The son, the second child, now five years of age, has had multiple ecchymoses constantly appearing all over his body since he first began to creep. The larger lesions have occurred following trauma, often of a trivial sort, but many small, nonpetechial, purpuric lesions have been present intermittently. His first nosebleed occurred at the age of twenty-two months, subsequent to an injury. It lasted twenty-four hours. Since then he has had one severe nosebleed and numerous ones of short duration. He has not bled abnormally from minor injuries. At the age of six months he had bronchitis, and since then he has had several attacks of tonsillitis and frequently "colds" which were not accompanied by an increase of purpuric skin lesions.

The child has a slight degree of hydrocephalus. At the age of sixteen months when he began to walk, neuropathologic signs and symptoms were noted. It then became recognized that these were probably due to hemorrhage from a birth injury. In spite of his illnesses, the boy is well developed and intelligent. At the age of two the bleeding time was over forty-five minutes, when the blood coagulation time, clot retraction, numbers of blood platelets and tourniquet sign were normal.

Recently an accident caused a fracture of his skull. Three weeks later a decompression operation was performed and extradural and subcortical bloodclots were removed. These clots are attributed to the recent injury. The bleeding time was found normal about a week before the operation, but when tested on two different days shortly beforehand, it was over two hours in length. At these times the blood clotted, and its clot retracted, normally. The blood platelets were morphologically normal and the numbers were slightly increased above normal. There was a slight degree of simple anemia. Transfusions of about 150 cc. of blood were given about twelve hours before and directly after the operation. About an hour prior to the second transfusion the bleeding time was forty-five minutes and of a similar duration the next day when the bleeding from the puncture by a sharp needle was controlled by pressure. In the following month the bleeding time was tested on five different days and was always much prolonged, measures usually being taken to stop the bleeding after from twenty to forty-five minutes. During this month the blood platelets were found in at least normal numbers, and the hemoglobin and red blood cells increased to normal. The operation was accompanied by no abnormal blood loss, nor was there any abnormal bleeding from the wound during convalescence. It seems plausible to believe that there would not have been bleeding due to the operation even if

there had been no transfusions of blood. This is suggested because the bleeding time did not appear to be influenced by the transfusion, and the purpuric skin lesions continued to appear and disappear.

Three members of a second family—a man and his son and daughter—have shown the same hemorrhagic condition as the two members who were studied, belonging to the family mentioned above. There have been no other children, and the mother has had no abnormal blood loss. The father, now 31 years of age, does not recall that his parents or their relatives suffered from any type of recurrent hemorrhage. He, however, has always bruised very easily and relates that on "practically any day since I was a young child I have had a black-and-blue spot on my skin, and often many at one time." These lesions have decreased in numbers and size in the past six years, so that where formerly it was common to find a dozen or more large ones at any one time, two or three small lesions are now the rule. His bleeding time two and three years ago was from twenty to thirty minutes, but one year and also six months ago was normal. The blood clotted normally and the numbers of blood platelets were normal, and he has shown no other abnormalities than those noted. As a youth he had teeth extracted and underwent an operation for hernia without the occurrence of any abnormal blood loss.

This man's son, aged eight years, has been observed frequently in the past three years. This child has had, since the age of a few weeks, many "black-and-blue spots" on various parts of his body. Sometimes for weeks there have been a great many; at other times and even for months there have been few, and rarely, none. He has had no other hemorrhages except two slight nosebleeds. Apart from the purpuric lesions and a slight degree of anemia, he has appeared healthy and is well developed. Many sorts of examinations have been negative. Recently the purpuric lesions have tended to become fewer while he has taken a more liberal and broader diet than formerly. His bleeding time has sometimes been an hour, often thirty minutes, on other occasions about ten minutes, and several times, it has been found normal. There has appeared to be no definite relationship between the prolongation of the bleeding time and the occurrence of the purpuric lesions, although the bleeding time has not been over ten minutes when ecchymoses were few or absent.

The daughter, aged two years, has rickets and slight secondary anemia. She, too, has had since the age of a few weeks the repeated appearance of purpuric lesions in her skin. She has had one severe nosebleed. Recently she has partaken of a well-balanced adequate diet and her health has improved, and perhaps the ecchymoses have become fewer. Her bleeding time, tested on three occasions some months apart, has varied from twenty to forty-five minutes. Her blood platelets have never been decreased nor the coagulation time of her blood prolonged.

None of these five patients who has been studied has had any petechiæ or crops of small purpuric lesions such as occur with considerable regularity in people with thrombopenic purpura. Likewise application of a tourniquet to the arm, shutting off the radial pulse for three minutes, has not produced purpuric lesions well below the place of constriction, as is the rule in purpura hemorrhagica. Nasal telangiectases have not been present, and there is no definite evidence that the patients have suffered from any spontaneous internal hemorrhages.

A surgical operation undertaken in the face of a distinct prolongation of the coagulation time of the blood or marked reduction of the blood platelets usually will be followed by oozing of blood for many hours and sometimes for days. An exception should be made for the operation of splenectomy for chronic thrombopenic (thrombocytopenic) purpura because removal of the spleen in this condition permits changes to occur that cause hemorrhage to cease. It is, thus, of interest to note that some of these five patients with a prolonged bleeding time, but with at least a normal number of blood platelets and blood that clots in normal time and a clot that retracts promptly, have undergone surgical operations without abnormal blood loss.

This type of hemorrhagic diathesis appears to be relatively mild and tends to be outgrown. However, its etiology, the reason for the prolonged bleeding time, and the tendency for this to be demonstrable intermittently remains obscure.

Dr. Thomas E. Buckman informs me that he has observed several cases in young children comparable to the ones described above. His report concerning them follows this paper. Two were those of a brother and sister. His cases have not occurred in parents and offspring, nor as yet have been observed to continue into adult life. The condition of some of his cases has been distinctly more serious than that of the five recorded here; the death of at least one is attributable to the hemorrhagic condition.

Summary.—There exists a chronic familial hemorrhagic condition characterized by a prolonged bleeding time in the absence of a decrease of blood platelets and a delayed coagulation time of the blood. Multiple ecchymoses and recurrent epistaxis are characteristic symptoms. Pathologic blood loss and abnormal bleeding time may be present at one time and not at another, but their occurrence is not necessarily synchronous. This hemorrhagic condition appears in infancy and may extend into adult life, but then its severity tends to decrease and the condition may disappear as the patient grows older.

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ATYPICAL PATHOLOGIC HEMORRHAGE IN EARLY LIFE.

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It is now well established that prolongation of the bleeding time occurs quite generally when the number of blood platelets in the circulating blood falls below a level of about 100,000 per c.mm. Hence, a prolonged bleeding time may be observed in any condition accompanied by marked thrombopenia, such as occurs in idiopathic thrombopenic purpura, aplastic anemia, lymphatic leukemia and pernicious anemia, among other conditions. Moreover, it is generally supposed that prolongation of the bleeding time rarely occurs unless there is marked diminution in the number of blood platelets. On the other hand, marked prolongation of the coagulation time occurs quite constantly in hemophilia in which disease the blood platelets appear to be qualitatively defective but numerically sufficient and the bleeding time is usually normal. By means of blood examinations, therefore, it is possible to differentiate hemophilia, thrombopenic purpura and nonthrombopenic purpura.

In following the course of any considerable number of cases showing pathologic hemorrhage, it becomes evident that abnormalities of the bleeding time are observed in conditions other than thrombopenic purpura, and that prolongation of the coagulation time occurs in individuals who certainly do not have thrombopenic purpura or hemophilia. Thus, prolonged bleeding time or prolonged coagulation time, or both, may occur in such conditions as severe and long-continued obstructive jaundice, "anaphylactic shock," hemorrhagic disease of the new born and erythremia. The cases briefly described below are reported as further instances of pathologic hemorrhage which do not conform to any of the well-recognized types of disturbance of the coagulation mechanism.

Case Reports. Case I.—This patient, a girl aged three years, was first admitted to the Boston City Hospital June 19, 1923, following a fall which caused her to bite her tongue. Uncontrollable bleeding from the tongue followed in spite of local applications, and this was stopped only after a transfusion of blood.

There was a positive family history of hemorrhagic diathesis on the father's side. The paternal great-grandfather, grandfather, four paternal uncles and one paternal aunt, the father himself, and the brother of the patient all showed a tendency to bleed unduly from any wounds.

This child had had frequent and severe nose bleeds since one and a half years of age. Six months before entrance to the hospital she had a severe hemorrhage from a cut on the upper lip.

The physical examination on admission showed a well-developed and well-nourished child almost comatose, very pale, bleeding freely from the

mouth. The pulse was 180 and almost imperceptible. A scar 1 cm. long was present on the tip of the tongue. An apical systolic murmur was present. The physical examination was otherwise not remarkable. This patient remained in the hospital about a month, during which time she received four transfusions of whole blood. After the first transfusion the bleeding stopped and did not recur. The other transfusions were given for the relief of anemia, and the patient made an uneventful recovery.

After discharge from the hospital the child's history, except for occasional nose bleeds readily controlled by packing, was uneventful until five days previous to her second admission, two years after her first admission.

Five days before her second admission she sustained a cut of the hard palate from the use of a spoon, and bleeding from the cut had continued throughout this time.

Physical examination showed an almost comatose child, markedly pale, breathing rapidly, the mouth containing much blood. The skin over the abdomen, back and extremities was covered with large ecchymotic areas, never present before. The apical systolic murmur, noted at the first examination, was still present. The physical examination was not otherwise remarkable. She remained in the hospital fifteen days, during which time she received two transfusions of whole blood. During her stay in the hospital she improved definitely, and the bleeding from the mouth stopped entirely. Shortly after admission, however, bleeding from the nose occurred and continued at intervals. The family were unwilling to leave her in the hospital for furthur transfusions and she was discharged against advice, somewhat improved but clearly still suffering from a serious disturbance of the coagulation mechanism. Unfortunately the further course of the case is unknown.

On both occasions during which this unusual case was under observation every possible attempt was made to determine the cause of bleeding but without success. The blood Wassermann test was negative, and the usual examinations of the stools and urine showed no abnormality. She occasionally had slight fever, but no other evidence of infectious disease could be found.

At her first admission, the hemoglobin was 40 per cent; the red blood cell count was 2,500,000 per c.mm.; and the white cell count was 16,000 per c.mm. No abnormal leukocytes were seen. On discharge, the red cell count had risen to 3,500,000 per c.mm., and the hemoglobin, to 68 per cent. On admission the blood platelet count was 680,000 per c.mm. and the bleeding time was thirty minutes. The coagulation time was forty-five minutes. (With the technique used, method of Lee and White, the coagulation time of normal blood is not over twelve minutes.) At the end of her first stay in the hospital the blood platelet count was still elevated, 500,000 per c.mm.; the coagulation time of the blood was twenty minutes (method of Lee and White); and the bleeding time, fifteen minutes The blood clot was firm and retracted normally in each instance.

On admission to the hospital the second time, the hemoglobin was 16 per cent; the red cell count, 1,150,000 per c.mm.; the white cell count, 21,400 per c.mm.; the differential count was normal; the bleeding time was over thirty minutes; the coagulation time, twenty minutes (method of Lee and White). At this time, unfortunately, no platelet count was obtained, but from inspection of the stained blood specimen it was observed that blood platelets were present in abundance. On discharge the red cell count was 2,400,000 per c.mm.; hemoglobin, 64 per cent; white cell count, 9400 per c.mm.; differential count, normal; the blood platelet count, 600,000 per c.mm.; the coagulation time, ten minutes (method of Lee and White). But there was still oozing from the nose, and ecchymoses were present over the body.

Comment. This case presents the following remarkable features. 1. There is an atypical family history of bleeding; that is, the disease was exhibited both in males and females, and transmitted apparently by males. This, of course, is unlike hemophilia although atpyical family histories in hemophilia have frequently been reported.

2. The occurrence of undue bleeding after trauma in a female with an excessive number of blood platelets and prolonged coagulation time is unusual. Dr. R. C. Teft made a special study of the blood platelets in this case on her first admission to the hospital. He found that a suspension of blood platelets obtained from the patient would cause the coagulation of blood from a patient suffering from hemophilia in the same time, fifteen minutes, as was required for a suspension of normal blood platelets to clot the hemophilic blood. In other words, the blood platelets *per se* both qualitatively and quantitatively were normal, so far as could be determined. This finding is unique.

3. The prolongation of the bleeding time in the face of a normal number of blood platelets, in a case showing no evidence of liver damage, allergy or infection, is also unusual. The presence of a firm clot and good clot retraction is evidence that there was no diminution of fibrinogen.

Case II.—This patient was the brother of the patient whose case is recorded above as Case I. He entered the Boston City Hospital when four years of age, November 3, 1921. There had been a history of epistaxis since two and a half years of age, for which complaint he was admitted at this time.

The physical examination showed oozing from the nose and numerous ecchymoses over the body in a pale, dyspneic child. Otherwise the findings on physical examination were not remarkable. He remained in the hospital at this time about a month, during which period there was occasional hemorrhage from the nose in spite of transfusion.

The patient died December 17, 1921. Unfortunately there was no autopsy.

During the eighteen months previous to death, this child was frequently examined both clinically and from the point of view of the blood. No definite diagnosis was ever made, but it seemed clear that syphilis and other infectious diseases could be ruled out. The patient had essentially the same type of disturbance of the coagulation mechanism as his sister; that is, ecchymoses and a tendency to bleed unduly from slight trauma.

The blood findings were consistent with those of anemia due to blood loss, except that in spite of an abundance of blood platelets, there occurred throughout a prolonged bleeding time, and normal or slightly prolonged coagulation time; 26 complete blood examinations including hemoglobin, red cell count, white cell count, differential count and platelet count were made. There were also ten observations on the coagulation time. The data are not included as the blood histology never showed anything more than changes which could be accounted for on the basis of blood loss and these changes were not marked. In other words, at times there would be a reduction of the hemoglobin to 70 per cent, and the red cell count to 4,000,000, a very slight leukocytosis of perhaps 14,000, with a normal differential count and normal or slightly elevated platelet count (that is a count ranging

from 300,000 to 600,000). The red cells showed simply achromia and some slight variation in shape. Rarely a blast was seen. Sometimes the proportion of reticulocytes would rise to 5 per cent.

CASE III.—This was a boy three years of age, admitted to the Children's Hospital April 6, 1925 for the relief of epistaxis. There was no family history of hemorrhagic diathesis. This patient previously had had numerous nose bleeds following slight trauma.

On admission to the hospital, physical examination showed a well-developed and well-nourished white boy, aged three years, oozing blood from the nose. There was an apical systolic murmur, and an ecchymotic area over one leg; otherwise the physical examination was not remarkable. During his stay in the hospital he received three transfusions of blood, which was the only effective means of stopping the epistaxis. Subcutaneous and intramuscular injections of "Fibrogen" (Merrill Company), and intramuscular injections of human blood were apparently without effect on the course of the disease.

On admission, the hemoglobin was 18 per cent; the red cell count, 1,100,000 per c.mm.; the stained specimen of blood showed a polymorphonuclear leukocytosis with a great increase in the blood platelets. The bleeding time was longer than one hour, and the coagulation time was six minutes (Capillary tube method. With the technique here used the normal coagulation time is three to four minutes.) After one of the transfusions the bleeding time diminished to twenty minutes, but promptly increased again to longer than one hour. On discharge from the hospital, the hemoglobin was 67 per cent, and the red cell count was 4,200,000 per c.mm., but the bleeding time was still greatly prolonged, and there existed the same disposition to epistaxis although his general condition had greatly improved since admission.

Comment. Although every attempt was made to determine some cause for the hemorrhages in this case, the various examinations made showed nothing which could possibly be construed as the cause of pathologic bleeding. The case differs from the first two only in that there is no family history of hemorrhagic diathesis.

CASE IV.—A nine-month's old, male, white infant, weighing 15 pounds 10 ounces, was admitted to the Infants' Hospital June 22, 1925 with the complaint of restlessness and pallor. The family history was unimportant. This baby was normal at birth and had been breast fed. He had had numerous upper respiratory infections. Two months previous to admission following a "cold in the chest," the mother noticed that an unusually white color of the skin developed and that he had lost weight.

On admission, physical examination showed a pale, irritable, dyspneic boy. There were petechiæ over the legs. Pus was discharging from both ears. Bilateral ankle clonus, a very rapid pulse and palpable lymph nodes in the groins were the only other abnormal physical findings.

During the patient's stay in the hospital, there occurred frequent nose bleeds and loss in weight. Two transfusions were performed, following which the bleeding from the nose ceased, but the ears continued to drain, and the temperature remained elevated. Four weeks after entering the hospital the infant was withdrawn from the hospital by the parents against advice.

Many observations on the blood were made. On admission, the hemoglobin was 30 per cent; the red cell count, 1,000,000 per c.mm.; white cell count 7900 per c.mm. The blood platelets were normal in numbers, and remained so, or slightly increased, throughout his stay in the hospital. The

bleeding time varied from eighteen to twenty-five minutes. The coagulation time was five minutes (capillary tube method) on one occasion when the bleeding time was twenty-five minutes and the blood platelets abundant.

Comment. This case differs from the preceding three cases in that there was present recurrent upper respiratory infection with, finally, bilateral otitis media. It is quite possible that, in this case, the infection was in some way responsible for the disturbance of the coagulation mechanism.

Case V.—A white female infant, aged six months, was seen for the first time on March 1, 1927. There was no family history of hemorrhagic disease. The past history of this infant was that of a normal breast-fed baby. The present illness began about February 14, and was characterized by pallor followed by ecchymoses which successively involved almost the entire body. On examination, the patient appeared well developed and well nourished, but was partially comatose, pale and dyspneic. There was slight edema of the ankles. There was an apical systolic murmur. Numerous ecchymotic areas appeared over the abdomen, and evidence of older hemorrhage into the skin were present over the back, chest and extremities. Physical examination was otherwise negative.

Examination of the blood showed the following: Hemoglobin, 40 per cent; red cell count, 2,000,000 per c.mm.; white cell count, 8000 per c.mm.; differential count, normal; blood platelet count, 500,000 per c.mm.; bleeding time, over thirty minutes; the coagulation time (capillary tube method), ten minutes. Twelve hours later the patient had a convulsion with bulging fontanelle. Lumbar puncture gave a blood-tinged fluid. During the next twenty-four hours, several convulsions occurred, and the patient died thirty-six hours after she was first seen. The Wassermann tests on the spinal fluid and blood were negative. There was no autopsy.

Comment. The question arises whether or not these five cases are atypical varieties of idiopathic nonthrombopenic purpura. Also, is it to be assumed that they constitute a disease entity not hitherto recognized, or that the findings represent merely functional disturbances of the mechanism of blood coagulation dependent on some one or more etiologic factors which could not be determined at the time the cases were observed? Conclusions are not drawn from the observations on these cases, and they are reported in the hope that the subject may be given further investigation. Dr. George R. Minot has observed cases comparable to these, and his report concerning them appears in this issue of this Journal.

Summary. Observations on five cases of purpura in infants are presented in this report. The remarkable feature of each case was the occurrence of both prolonged bleeding time and prolonged coagulation time in the presence of a normal or slightly elevated blood platelet count. In no case could a satisfactory explanation of the dyscrasia be found. In one case it was clearly demonstrated that the blood platelets were capable of causing the clotting of hemophilic blood as rapidly as the blood platelets of a normal individual,

thus suggesting that the condition is not allied to hemophilia and that prolonged coagulation time may occur in the presence of an apparently normal platelet picture. The number of cases is too small, however, to warrant the drawing of conclusions concerning the nature of this disturbance of the coagulation mechanism.

NOTE.—I am indebted to Dr. Kenneth D. Blackfan for permission to publish the cases from the Infants' and Children's Hospitals, and to Dr. Martin J. English for permission to publish the 2 cases from the Boston City Hospital.

RESULTS OF LIVER FEEDING IN PERNICIOUS ANEMIA.

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THE results of liver feeding in pernicious anemia, as used by Minot and Murphy,[1] have been so remarkable in certain instances and so uniformly successful throughout the past year in all of our patients suffering from this hitherto fatal condition that a report of their progress seems worth while. It may be pointed out that this clinical usage followed the carefully controlled study of factors influencing blood formation undertaken by G. H. Whipple[2] in 1920, which demonstrated the superiority of liver and kidney feeding in the recovery from anemia due to blood loss. In clinical practice, however, this diet is of greatest value in primary anemia. In fact the response in true Addisonian anemia is so prompt and characteristic as to distinguish it from severe secondary anemias in which the response is often indefinite or negligible.

The usual course on liver feeding is illustrated by the chart of the data of S. J. (Chart I). During the entire period from March until after his recovery from anemia in October, he was under constant observation in the hospital. From his admission until August he received eight blood transfusions and the usual therapy directed toward stimulation of blood formation, namely, cod-liver oil, heliotherapy and subcutaneous injections of iron, but there was progressive deterioration of his general condition, marked glossitis, atrophy of muscles, posterior-cord degeneration and extreme mental depression. During this unintentional control period, vitamins from cod-liver oil and fruit were given in large amounts. There was only a slight and transient increase of the blood following the transfusions. The work of Whipple, and all clinical and analytical work since, has demonstrated that the effective factor is not a special diet or an arrangement of dietary factors but is a definite fraction of liver and kidney which has been chemically identified and demonstrated to

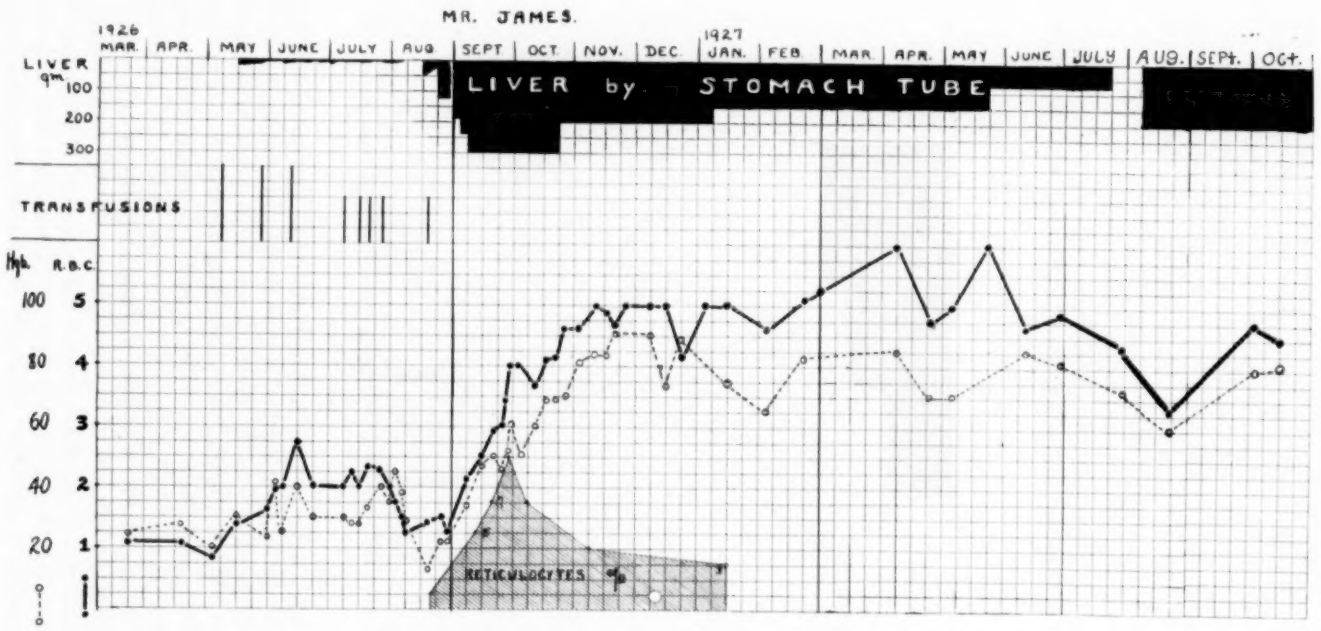
MR. JAMES.
1926
MAR.
APR.
MAY
JUNE
JULY
AUG.
SEPT.
OCT.
NOV.
DEC.
1927
JAN.
FEB.
MAR.
APR.
MAY
JUNE
JULY
AUG.
SEPT.
OCT.
LIVER gm
100
200
300
LIVER by STOMACH TUBE
TRANSFUSIONS
Hgb.
R.B.C.
100
80
60
40
20
5
4
3
2
1
RETICULOCYTES %

CHART I.

contain no vitamins according to present method of study. About the first of September he was given liver by stomach tube with the result that in five weeks the blood count rose from 1,200,000 to 4,000,000. Soon after starting this procedure, the blood showed what is now recognized as the most characteristic reaction of pernicious anemia to liver feeding, namely, an increase of the percentage of reticulocytes found in the smear, reaching in this case 10 per cent. The general condition improved in direct proportion to the rise of blood count. Glossitis, which had been very severe in August, disappeared during the first ten days of September, that is, before any

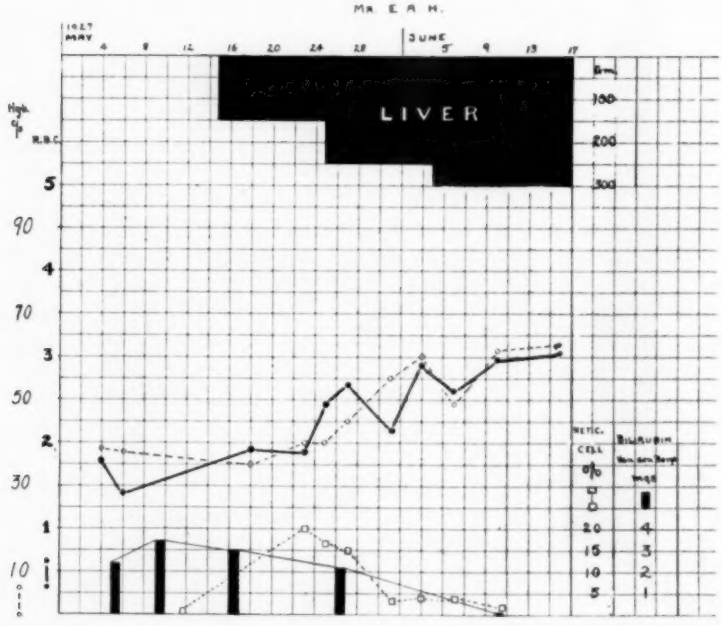

CHART II.

great increase in the blood count had occurred. The spinal-cord lesion was for the time being masked by the rapidly increasing strength of the skeletal muscles. In the spring, however, in spite of a blood count rising to 6,000,000, the effects of a combined degeneration of the spinal cord became gradually more evident, until in August a definite degree of spasticity could be elicited. It is most instructive for the management of other cases to note that in June and July of this year, discouraged by the increase of cord symptoms, he very much decreased and for the time being discontinued the ingestion of liver, and that during these months his blood count fell to 3,400,000 and there was a definite return of glossitis. This occurrence demonstrates that the

factors producing pernicious anemia are still present after ten months of liver feeding. Since the first of August he has again taken over 200 gm. of liver a day faithfully, with the result that his count is now 4,700,000 and the glossitis has disappeared with the exception of a few very slight areas. The condition of the spinal cord is slightly worse according to clinical standards.

The characteristic changes in composition of the blood in pernicious anemia treated by liver feeding have been accurately described by Murphy, Monroe and Fitz.[3] These are illustrated in the following case (Chart II). This patient had a rather marked jaun-

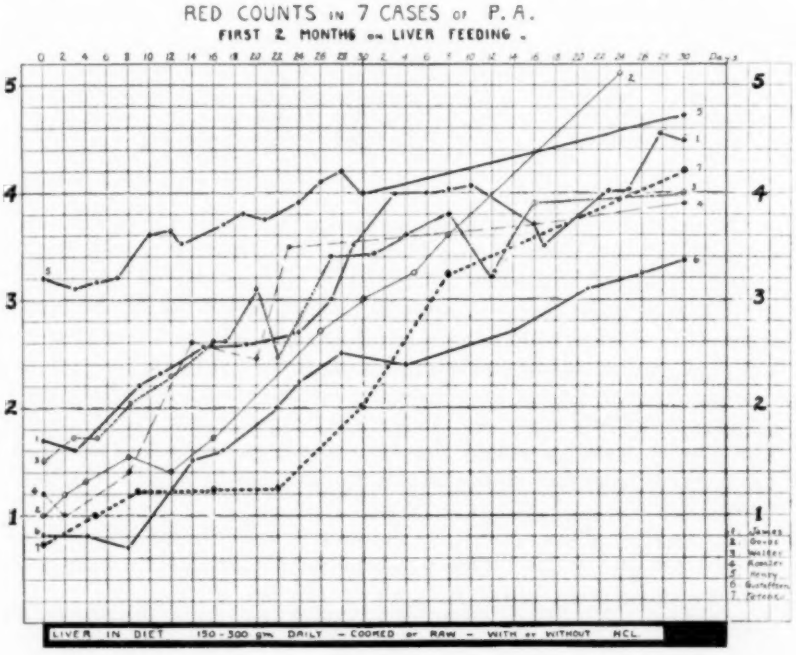

CHART III.

dice measuring over 3 mg. of bilirubin in the blood, the van den Bergh test being indirect. During the first four weeks of liver feeding this jaundice rapidly decreased, indicating the cessation of blood destruction and the elimination of excess pigment, until the van den Bergh reaction was nearly absent. During the first eight days the percentage of reticulocytes in the smear rose from less than 1 to the very high value of 20 per cent, and then rapidly decreased to a normal figure. This period of reticulocytosis is a constant finding in pernicious anemia during the first ten days of liver feeding as has been shown by Murphy, Monroe and Fitz. The crystal-violet vital stain for reticulum is used. During this

time the blood count was gradually rising so that at the end of ten weeks it reached 4,000,000.

TABLE. I.—PROGRESS OF PERNICIOUS ANEMIA ON LIVER FEEDING.

Patient.	R. B. C. before liver.	No. of weeks to attain R. B. C. of 4 million.	Present count, September, 1927.	Duration of diet.	Comments.
1. Mr. L.	2,250,000	not observed	3,840,000	14 mos.	4,790,000 at 4 mos.
2. Dr. M.	2,100,000	6	6,310,000	11 mos.	Very faithful
3. Mrs. W.	1,500,000	7	4,220,000	8 mos.	
4. Mrs. K.	1,000,000	6	4,500,000	7 wks.	Patient not coöperating
5. Mr. H.	3,000,000	5	4,170,000	5 mos.	
6. Mr. G.	1,000,000	5	5,500,000	8 mos.	
7. Mr. G.	900,000	7	5,510,000	5 mos.	
8. Mr. F.	900,000	7	4,560,000	6 mos.	
9. Rev. H.	1,710,000	10	4,010,000	3½ mos.	
10. Mr. J.	1,200,000	5	4,700,000	13 mos.	See chart

The uniformity with which an increase of blood count in pernicious anemia may be expected after beginning liver feeding is well illustrated by the curves plotted in Chart III. There may be, as shown in several of these cases, an apparent latent period for as much as eight days, during which there is no increase in the blood count, but even during this period rapid reorganization of blood formation is going on as indicated by the changes in the smear, especially the appearance of reticulocytes. Following this period the blood count increases to such an extent that in every instance it has reached 4,000,000 in from five to ten weeks, the average being about seven weeks.

The amount of liver necessary to produce these results is approximately 200 gm. a day. One patient, Dr. M., seemed to have an entirely satisfactory result with about 125 gm. a day. Mr. S. J. definitely became worse on about 75 gm. a day. Frequently very good results are obtained with 300 gm. The liver, either beef or calf, may be cooked in any way. It is, however, probably best for psychologic reasons to administer it as a medicine three times a day between meals in the form of a purée, which is rendered entirely liquid by being passed through a fine strainer. This may be mixed with or followed by orange juice to suit the taste. Raw liver may be taken in this manner. The addition of dilute hydrochloric acid to the meal, while occasionally beneficial in the control of gastrointestinal symptoms, was found unnecessary to the production of the typical remission in two extreme cases. The diet in addition to liver is a general one.

That the remission of the anemia is not transient is demonstrated in the following table. In all those patients who have been followed

and who have continued to take liver daily the blood count is more than 4,000,000, and there is little evidence of anemia. As has been shown by Minot, it is necessary to continue to take liver indefinitely; probably an average of more than 100 gm. a day is necessary to prevent the return of anemia. No effect on advanced spinal-cord degeneration has been produced in the two cases with serious symptoms from this condition that we have observed. The return of anemia and glossitis in the first case described is ample evidence that the essential pathogenic mechanism has not been removed by liver feeding. Nevertheless, there is no indication in this series that this diet will not protect the patient indefinitely.

Summary. Liver feeding in pernicious anemia is uniformly followed by recovery from anemia. This process is accompanied by two unique features, namely, rapid decrease of bilirubinemia and transient, sometimes marked, increase of reticulocytes. Anemia returned in 1 case at the end of ten months when liver was discontinued. Ten cases under observation from three to fourteen months now show no evidence of anemia. Advanced spinal-cord degeneration is not altered by this recovery of the blood. The recurrence of glossitis and anemia when liver feeding was discontinued at the end of eleven months indicates that the underlying pathologic condition is still present.

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CHRONIC APLASTIC ANEMIA AND SYMPTOMATIC HEMORRHAGIC PURPURA PROBABLY DUE TO BENZOL POISONING.

A Case Report.

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Accurate differential diagnosis in the field of blood dyscrasias is difficult. Although many diagnostic methods are available, the diagnostician is often only able to place a given blood disorder in a group containing similar conditions. Even with the more recently

developed technical aids absolute identification is too often impossible. More carefully studied cases are needed to clear away the obscurity surrounding the blood dyscrasias. The following case which is reported in some detail affords an interesting problem. The extensive laboratory data together with the clinical observations accumulated over a considerable period provide ample material for study.

Case Report. T. S., a white male, aged twenty-five years, teacher, presented himself September 25, 1926 with the complaint of "anemia" and intermittent bleeding from the gums of about two years' duration. His family history was negative as regards any blood disorders. The patient had had the so-called childhood diseases. At the age of twelve he had "pseudotyphoid fever" which lasted sixteen days. He stated that he had no bowel movement for fourteen days during this period. He has had repeated attacks of "flu," colds and bronchitis.

Present Illness. Aside from a rather obstinate constipation from 1913 to the present time, the patient's only illness has been intermittent attacks of colds and bronchitis. In 1918 he was constipated for five days during which time his "gums and mouth" swelled so that he could not eat. He was relieved by several doses of Epsom salts. In the spring of 1923 he noticed that little pinches and bruises had a tendency to remain as faint ecchymoses and were noticed by his room mate. He explained this on the basis of his fair complexion. He said exposure to the sun never caused him to tan. He would blister and reblister but his skin always remained fair and white. He never did perspire freely.

In the spring of 1924 he scratched the inside of his nose with his finger nail and it bled slowly for several hours. He consulted a doctor who told him that he had a nasal growth that should be removed. At this time he was treated locally and the bleeding stopped. Two weeks later he reported for the operation and was told that the growth had disappeared. The specialist, however, removed an "enlarged bone." There was some oozing following the operation but after the removal of the pack about twenty-four hours later there was no further bleeding.

He noticed also in the spring of this year (1924) that upon brushing his teeth his gums had a tendency to bleed. His dentist told him that his gums were in good condition but tender. After using a soft tooth brush and salt water this trouble ceased. From April to June, 1924, he felt "bad" in the afternoons and had some headaches, and a poor appetite. He attributed these symptoms to personal worry which was excessive at that time. Following a little rest and the use of a tonic he regained his appetite and gained 10 pounds in weight.

In June, 1924, he went to work in an oil refinery in Oklahoma. The first three weeks were spent in doing manual labor such as digging ditches mixing concrete by hand, and so forth. For the first three days he tired very easily but soon became accustomed to the work and noticed no particular fatigue. After three weeks of this work he was transferred to the laboratory where his routine work consisted of testing the viscosity of lubricating oils. He stated that there were several windows in the laboratory. They were seldom opened because he was instructed to allow no draft to pass through the room which might interfere with the viscosity work. At the end of each day the testing machines were filled with benzene or benzol. When working at high temperatures, the mixtures would boil viciously and considerable vapor was constantly about his face. After a time the high temperature testing machine (210° F.) became inaccurate.

He recalibrated it and then watched it very closely, washing it with benzene several times a day to insure accuracy.

In November of the same year he developed "flu," which confined him to bed for one week. This was followed by a deep cough for which he consulted a doctor, thinking the fumes might have caused some lung trouble. The doctor assured him that his lungs were "clear." A radiogram of the chest showed no lesions. He was told that he was run down.

In the latter part of December, 1924, and first part of January, 1925, he noticed that his gums would bleed when he brushed his teeth. He again used the salt solution and soft tooth brush which this time gave him no relief. He washed his teeth less often. During this winter he cut his cheek while shaving and it bled for some time, stopping only after he had visited a druggist and had something applied to the wound. At this time he also noticed various blue spots over his body that he could not explain.

In April, 1925, he began looking badly and a friend asked him if he had jaundice. During the summer of 1925 he experienced severe headaches of a pulsating type, noticed especially during exertion. He also noticed that he was very weak. In August a doctor whom he was visiting in Oklahoma for antityphoid injections suggested that he might have some trouble with his blood and recommended a blood count. He returned to Texas, however, for a two-weeks' vacation, suffering most of that time from an attack of bronchitis which had its onset during his railway journey.

When he returned to Oklahoma he had a blood count made on September 22, 1925. The blood was drawn from his ear and the puncture wound continued to bleed for one hour and thirty minutes. The red cell count was 1,200,000, with a color index of 1.2. His doctor treated him with sodium cacodylate and following each injection his arm would bleed rather freely. During this time his gums bled when he brushed his teeth and he quit brushing them altogether. From November to December, 1925, his gums bled every night and he would spit out large clots of blood every morning from two or three bleeding areas on his gums. In December, 1925, he resigned his position and returned to Texas. He improved for a couple of months and gained 17 pounds.

In March his red blood count was 1,250,000. A diagnosis of pernicious anemia was made and he was sent to another town for a transfusion. His first transfusion was done on April 4, 1926 and his count at that time was 1,760,000 with a color index of 1.3. He received altogether six transfusions, the last being given on August 30, 1926 at which time his red cell count was 2,560,000. (See table for all blood counts.) He stated that after his fourth transfusion his gums began to bleed more profusely and that they bled for twelve to forty-eight hours at a time. Nothing seemed to stop the bleeding. His bleeding time at the time of his third transfusion was one hour and thirteen minutes. Also, after his fourth transfusion he noticed for the first time many petechiæ, especially over his legs.

While on his way to another Texas town to take up his duties as a teacher in a high school, the patient was seen for the first time by the writer on September 3, 1926. His red blood count at that time was 2,150,000; color index, 1.4; white cell count, 3900; polymorphonuclear leukocytes, 66 per cent; small lymphocytes, 32 per cent; large lymphocytes, 2 per cent. The blood smear was negative except for slight alteration in the size and shape of the red cells and an occasional microcyte. There were no blasts noted in the smears. He was advised to return at the first convenient time for a careful diagnostic study.

He returned on September 18, 1926 and was admitted to Baylor Hospital stating that he had had some oozing from the gums.

Physical Examination. Patient appears to be about twenty-seven years of age, is 5 feet 10 inches tall, weighs 165 pounds, and appears well nourished

LABORATORY DATA ARRANGED IN CHRONOLOGICAL ORDER.*

Date.	†Hemoglobin, per cent.	R. B. C. in millions.	W. B. C. in thousands.	Poly., per cent.	Small lymph., per cent.	Platelets in thousands.	Transfusions.	Bleeding time in min.	Clotting time in min.
1925.									
Sept. 22	...	1.20							
1926.									
Mar. 21	...	1.25							
April 4	49	1.76	5.3	46	36	...	First	73	
15	...	1.95	...	...	...	...	Second		
25	...	3.39							
May 6	47	1.92	4.5						
17	55	3.40	5.3						
31	50	3.38	5.2						
June 2	...	2.70	...	...	...	...	Third		
12	...	3.28	...	...	...	...	Fourth		
28	55	3.72	6.0						
July 8	55	3.28	4.8						
12	...	2.08							
22	...	1.80							
28	48	2.00	5.0	...	...	...	Fifth		
Aug. 1	...	2.65							
30	53	2.56	...	...	...	...	Sixth		
Sept. 3	60	2.15							
18	55	2.68	5.5	48	44				
20	50	2.35	5.1	49	45	420	...	12	4½
21	...	...	...	...	...	320	...	7	
23	...	...	...	...	...	...	260 cc.		
24	60	2.93	5.0	50	48	...	300 "		
25	65	3.02	7.5	63	32	...	300 "		
26	70	3.25	6.0	67	27				
30	70	3.60	5.3						
Oct. 9	70	3.65	4.3	68	31	205			
30	62	1.41	3.1	53	40	262	...	7	
Nov. 2	55	1.46	3.3	53	40	...	280 "		
3	55	1.92	4.7	53	40				
4	60	2.26	...	...	...	...	310 "		
5	67	2.44	4.7	58	40				
6	...	...	...	...	...	...	260 "		
8	71	3.16	7.1	65	32				
9	65	...	...	...	...	212	275 "		
10	70	3.32							
11	70	2.79	...	...	...	190	160 "	14	3½
12	65	2.68	5.9	60	36	196			
13	...	...	...	...	...	...	360 "		
14	60	2.49	...	...	...	...	230 "		
15	65	2.76	...	...	...	198	260 "	7	
16	70	3.12	...	...	...	...	325 "		
17	70	3.17	7.0	59	37	...	420 "		
17‡	70	3.36	...	...	...	220			
18	65	3.24	11.3	75	20				
19	65	3.12	11.6	74	23	230	...	3	
22	55	2.88	8.3	67	30	...	300 "		
23	65	3.10	5.3	65	31	...	...	6½	
26	65	3.25	7.6	67	28				
29	50	2.52	7.4	68	30	...	...	6½	
Dec. 3	55	2.37	6.9	63	30	240	...	6½	
6	45	2.14	10.0	72	24	...	300 "		
7	55	2.64	7.9	63	31				
11	60	2.54	9.5	65	34	218	...	11½	
13	55	2.47	6.6	65	34				
15	60	2.73	...	...	...	...	140 "	9	3½
17	55	2.20	...	...	...	...	...	10½	
18	...	...	...	...	...	...	330 "		

LABORATORY DATA ARRANGED IN CHRONOLOGICAL ORDER.*—
(Continued.)

Date.	†Hemoglobin, per cent.	R. B. C. in millions.	W. B. C. in thousands.	Poly., per cent.	Small lymph., per cent.	Platelets in thousands.	Transfusions.	Bleeding time in min.	Clotting time in min.
Dec. 20§	60	2.75	6.8	62	36	...	350 cc.		
21	65	3.24	...	...	...	...	...	5½	
21	60	2.96							
22	55	2.62	10.6	71	25				
23	50	2.34	...	...	...	...	350 "		
24	50	2.44	7.9	65	33				
26	50	2.28	9.0	60	38				
29	50	2.55							
31	50	2.40	...	...	...	...	275 "		
1927.									
Jan. 1	50	2.24							
3	50	2.41	6.9	64	35				
5	50	2.30	7.7	64	30				
11	51	2.21	6.9	62	29				
13	52	2.13	5.7	62	34				
17	48	1.98							
20	48	2.03	...	...	...	217	...	16	
27	47	2.02	...	...	...	...	500 "		
28	56	2.52	8.8	64	30				
Mar. 8	19	0.85	6.6	54	42	142	...	14	
9	40	1.20	7.9	60	35	...	550 "		
10	27	1.41	7.7	56	36				
11	47	1.93	...	...	...	...	580 "		
12	48	2.27	5.8	63	30				
14	41	2.48	8.0	60	34	...	490 "		
15	55	2.74							
16	59	3.01	...	...	...	...	550 "		
17	61	3.10	...	...	...	...	500 "		
19	60	3.11	...	...	...	...	550 "		
21	65	3.45	7.7	65	26				
22	...	...	...	...	...	...	400 "		
23	70	3.67							
24	70	3.50							
25	...	...	...	...	...	...	570 "		
26	70	3.61							
April 1	75	3.50	7.0	65	29				
4	65	3.00	7.4	62	32	...	...	4½	
5	60	2.81	...	...	...	...	425 "		
6	60	2.90	...	...	...	...	...	3½	
7	65	3.22	...	...	...	...	500 "		
8	70	3.57							
11	...	...	...	...	...	...	420 "		
12	60	3.04	7.2	63	30				
12	60	3.01							
13	60	2.93	...	...	...	...	310 "		
14	70	3.53	9.1	64	30	...	...	3	
15	60	2.84	...	...	...	...	320 "		
16	65	2.80	8.5	63	33				
17	65	2.75	...	...	...	...	295 "		
17	50	2.00							
18	60	2.72	7.8	61	35	...	340 "		
19	60	2.67	...	...	...	...	330 "		
20‖	65	3.04							
20¶	60	2.75							

* Numerous blood counts have been omitted from the table because of their minor significance.

† All hemoglobin estimations, except on very rare occasions, were done by the Sahli method.

‡ Splenectomy. § Tonsillectomy. ‖ 10 A.M. ¶ 3 P.M.

but slightly anemic. There are no noticeable physical deformities. He has thick, reddish hair. The hair distribution over his body is normal. His skin is fair, slightly translucent, warm and smooth. Over the legs, forearms and thighs, and occasionally about the face are noticed numerous petechiæ, some of which are apparently of recent origin. There are also seen numerous ecchymotic areas, especially about the extremities. The abnormal findings other than as noted are moderately pale conjunctiva, a small hemorrhagic spot about 1½ mm. in diameter on the sclera of the right eye, small submerged tonsils, slight hyperemia of the pharynx, teeth small and apparently unkept. Gums appear healthy. They are not spongy or diseased. Two or three small nonretractile clots of blood were noticed on the margin of the gums in the upper left molar area. A soft systolic murmur was heard in the pulmonic area. There was very slight tenderness over appendix. The edge of the spleen was just palpable on deep inspiration.

Laboratory Tests. The significant laboratory findings at this time were: red cells, 2,350,000; hemoglobin, 50 per cent; white cells, 5100; polymorphonuclear leukocytes, 49 per cent; small lymphocytes, 45 per cent; platelets 320,000; bleeding time, twelve minutes (Duke's method); clotting time, four minutes, thirty seconds; a nonretractile clot; fragility test showed complete hemolysis with 0.3 per cent salt solution, partial with 0.35 per cent and no hemolysis with 0.4 per cent (that is, an increased resistance). The icterus index was five. The Wassermann and Kahn tests were negative. The blood chemistry was normal. An Ewald test meal revealed a trace of blood, total acidity of 51 and free hydrochloric acid 15. A tourniquet test (60 mm. of mercury) produced an almost uncountable number of petechiæ below the blood pressure cuff within thirty seconds. Urinalyses were negative. Roentgen ray examination of the gastrointestinal tract was negative. Roentgenograms of the sinuses and teeth were negative except for a congenital absence of the frontal sinuses.

Course. Following three transfusions, the patient was allowed to return to his teaching with a red cell count of 3,250,000. He was put on a diet containing generous quantities of liver, kidney, rare beef, milk, eggs, fresh fruits and fresh vegetables. He was readmitted to Baylor Hospital on October 31, 1926. His condition had not improved. He had been bleeding intermittently from his gums and many new petechiæ had appeared. His count upon readmission to the hospital was 1,410,000; white cells, 3100; color index, 2.2; polymorphonuclear leukocytes, 53 per cent; small lymphocytes, 40 per cent; large lymphocytes, 4 per cent; transitionals, 3 per cent; the blood smear showed very occasional microcytes, a moderate number of macrocytes with only a slight change in the size and shape of the red cells. There were no blasts present. Bleeding time was seven minutes.

The patient was given ten transfusions at intervals of from one to three days and on November 17 a splenectomy was performed by Dr. G. D. Mahon.

Examination of Spleen. The spleen was moderately enlarged. The pathologic report was as follows: The specimen consists of the entire spleen; it measures 15 by 8 by 3.5 cm. and weighs 250 gm. The spleen is moderately firm in consistency and keeps its form when moved about. The splenic notch is prominent. The cut surfaces are moderately dry but no localized lesion or striking diffuse changes are apparent grossly. The Malpighian bodies are hyperplastic with well-developed germinal centers. The lymphoid tissues throughout the splenic pulp are more prominent than usual. The stroma cells of the pulp are only slightly hyperplastic but there is apparently a moderate excess of blood pigment in the pulp tissues. Moderate lymphoid hyperplasia of the spleen with slight hyperplasia of splenic pulp and increased blood pigment.

Subsequent Course. There was no improvement in his bleeding time and no apparent improvement in his red cell production. He was given five more transfusions and on December 20 his tonsils were removed. His condition showed no particular improvement and he was given three more transfusions and allowed to go to his home. He left the hospital with a blood count of 2,520,000; white cells, 8800; polymorphonuclear leukocytes, 64 per cent; small lymphocytes, 30 per cent; large lymphocytes, 4 per cent. His bleeding time a few days prior to his discharge was sixteen minutes. His progress was downward during his stay at home and he returned to Dallas, March 8, 1927. He was given during the next two weeks twelve more transfusions. During this time he occasionally bled rather profusely from his gums.

About April 12 the patient's urine became red colored and upon examination revealed blood cells. This became more marked each day and his urine became practically pure blood. On April 15 he complained of excruciating headaches, localized in the right frontal region. Large and frequent doses of morphine were required for relief. On the morning of April 20 he was a little stuporous but little attention was paid to this because of the morphine he had received. His red blood count on this morning was 3,040,000. About two o'clock of the same day he could not be roused. He was bleeding from the mouth and nose, bowel, and kidneys. Spinal puncture revealed uniformly bloody fluid which was otherwise negative except for small amount of globulins and an increased reduction. He died at 11.15 P.M., April 20, 1927.

Autopsy. An autopsy was performed by Drs. Geo. T. Caldwell and O. T. Woods. Their findings were as follows: Anatomical diagnosis: (1) Extensive hemorrhage into the right frontal lobe of the brain, with softening of the surrounding brain tissue; (2) diffuse hemorrhage into subdural and subarachnoid spaces; (3) distention of lateral ventricles with hemorrhagic fluid; (4) hemorrhage into the pelvis of both kidneys; (5) multiple suggilations beneath the visceral and parietal layers of the pericardium; (6) extensive hemorrhage into the retroperitoneal tissues and the mesentery; (7) multiple subserous hemorrhages into pleura and bowel walls; (8) multiple petechial hemorrhages and suggilations in skin, especially of face, chest wall and arms; (9) moderate edema of lungs; (10) healed splenectomy wound; (11) adventitious fibrous adhesions between diaphragm and left lobe of liver, and between the omentum and body wall; (12) partially clotted blood in the mouth; (13) multiple venesection wounds of the arms.

Microscopical Examination. Brain and meninges: cerebral hemorrhage and hemorrhage into meninges. Lungs: diffuse hemorrhages in pleura and into alveoli of lungs. Moderate emphysema of lungs. Hyperplasia of peribronchial lymphoid tissue. Heart: diffuse hemorrhages into pericardium and outer layers of myocardium. Moderate hypertrophy of fibers of myocardium. Kidneys: multiple small focal areas of chronic nephritis. Albuminuria and slight hematuria. Liver: slight chronic hepatitis, involving chiefly the portal areas. Pancreas: no noteworthy changes in pancreas. Bone marrow: there is a moderate increase in blood formation in the bone marrow of ribs and vertebra, but the fat is still well preserved. The focal hyperplastic areas are about equally divided into erythroblastic, leucoblastic and lymphoblastic types.

Comment. Summarily, the significant points in this patient's history and findings are as follows: No familial history of bleeding; exposure to benzene, following which symptoms actively developed; an anemia with blood smears consistent with a chronic aplasia of

the hemopoietic system; a practically normal free hydrochloric acid stomach content; normal clotting time; prolonged bleeding time; normal platelet counts; very sharp positive reaction to the tourniquet test; nonretractile bloodclots; decreased fragility of the red cells; a normal icterus index; a fairly constant leukopenia; bleeding from the gums, and as a terminal manifestation, from the kidneys and gastrointestinal tract, in fact a universal hemorrhage; and a generally negative physical examination except for a barely palpable spleen.

A differential diagnosis in this case is not easy. The group of diseases in which are included Banti's disease, Gaucher's disease, von Jaksch's disease, etc., may be ruled out by the absence of a markedly enlarged spleen and its histological appearance. Scurvy is eliminated by the absence of spongy, diseased gums. Hemophilia is excluded on the basis of a normal clotting time and a negative family history. The so-called simple chronic anemia with defective blood formation, caused by parasites, chemical poisonings, etc., is not so easily disposed of. Myelophthisic anemia can be ruled out by the absence of any evidence of neoplasm and bone marrow metastasis, by the blood picture and the autopsy findings. Idiopathic aplastic anemia may be excluded on the basis of the duration of this patient's illness. An aplastic anemia from some type of poisoning which may be closely related to the simple anemia mentioned above must still be considered a possibility. Idiopathic thrombocytopenic hemorrhagic purpura can be eliminated by the persistently normal platelet counts. Idiopathic hemorrhagic purpura is mentioned with reluctance. The writer feels that the term, hemorrhagic purpura, should be used only in combination with some word specifying at least the nature of the purpura as for example, thrombocytopenic hemorrhagic purpura. The patient's failure to improve following the splenectomy is against thrombocytopenic purpura. His normal or decreased fragility test and normal icterus index are not consistent with hemolytic jaundice. Finally, pernicious anemia must be considered. The absence of symptoms or signs suggesting a glossitis or disease of the central nervous system; the finding of free hydrochloric acid in the stomach contents; an icterus index of five (which is usually much greater in pernicious anemia); the patient's age and the course of disease, all are against pernicious anemia.

It seems that this patient's chief trouble lay in his capillary system but classification is difficult. In the absence of any other etiological factor, exposure to benzene fumes must be considered a possible cause, but it must be remembered that at least the tendency to bleed existed before this exposure. The laboratory and autopsy findings are consistent with chronic benzol poisoning.* Alice Hamilton[1]

* The reader is referred to the U. S. P. H. Reports (vol. **41**, Nos. 27, 28 and 30) for a comprehensive summary of benzene poisoning with bibliography.

has described a condition in which there is a solution of the endothelial cells of the capillary system produced by benzol poisoning. There is also in this condition an aplasia of the bone marrow, so that the absence of blasts in the smears is consistent with an aplastic process.

Conclusions.—It is believed, therefore, that the most tenable diagnosis for this case is chronic aplastic anemia with a symptomatic hemorrhagic purpura, probably due to benzene poisoning, in which the endothelial cells or the capillary system and the blood forming cells of the bone marrow bore the brunt of the chemical intoxication.

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FATALITIES FOLLOWING THE REINJECTION OF FOREIGN SERUM.

With Report of an Unusual Case.

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Fatalities following a reinjection of foreign serum are extremely rare, judging at least from the scarcity of such reports in the literature, and considering the large number of such injections given therapeutically. Lamson,[1] in a complete review of literature up until 1924 could find only 8 reported cases, and since then an additional one has been reported by Mendeloff.[2] Of these, 4 followed intravenous injections, and the others followed subcutaneous or intramuscular injections. Death following a first injection is comparatively more frequent and, though often wrongly ascribed to an anaphylactic reaction, is in reality due to the injection of horse serum into an individual who is either an asthmatic or who is naturally, or as Coca[3] terms it, "atopically" sensitive to horse serum.

In 1924, Hooker[4] warned against a second injection of serum because of the fact that he obtained positive skin reactions in patients who had previously received an injection of diphtheria antitoxin. Shortly after this, Park,[5] convinced, because of a large experience with second injections, that they were not dangerous, reinjected a large number of cases, in spite of the presence of a positive skin test, and, in no instance, did a severe reaction occur.

Because second injections of horse serum in a sensitized animal have caused death as a result of an anaphylactic reaction, by analogy many physicians have regarded fatalities or severe reactions

after serum injection as anaphylactic in character. We have, however, no acceptable proof or experimental evidence that such reactions in the human are the result of an antibody-antigen reaction, such as has been proven to occur in the rabbit or guinea pig; and, until such evidence is obtained, one is not justified in assuming that these reactions are anaphylactic in character. Reasoning in similar fashion, since sensitization in the lower animals, more particularly the rabbit, usually takes at least ten days, it has been assumed that any reinjection within this period is safe, whereas after the tenth day, such an injection is fraught with the danger of a reaction in a person sensitized from the first serum injection. If such an injection must be given, "desensitization" in a manner similar to that carried out by Besredka in the guinea pig has been advised, with the use of several different methods to prevent an anaphylactic reaction. Such measures presuppose an active sensitization from the first injection and the presence of an anaphylactic state; however, as has been stated above, since such a supposition is without scientific proof, the efficacy of such attempts at so-called "desensitization" is obviously doubtful. A careful review of the literature has failed to find anyone who has clearly proven the value of these methods of prevention; on the contrary, as will be discussed later, 3 instances of distinct failure are recorded.

It is not surprising, in view of these facts, that so much confusion and uncertainty should exist in the minds of the clinician as to the possible dangers of a reinjection of serum and the measures used to prevent them. When, in spite of what was thought at the time to be the proper method of prophylaxis, a fatality does occur, one is at a loss properly to account for it. Such an experience occurred recently in our medical wards and, because of its comparative rarity and the many interesting features which it presents, it has been deemed worthy of record.

Case Report. D. K. (Case No. 43406), a white female aged fourteen years, was admitted to the medical wards of the Mt. Sinai Hospital, service of Dr. H. B. Shmookler, February 17, 1927, complaining of weakness, precordial pain, dyspnea, and palpitation, with a history of an irregular temperature dating back several weeks. Past medical and family history were negative, particularly as to any evidence of hypersensitiveness. On examination, the important findings were: Pallor of the mucosae, heart rapid and forcible, but not enlarged, with a palpable thrill over the precordium, and a loud presystolic murmur heard best at the apex. Blood count showed a mild secondary anemia and moderate leukocytosis. Wassermann was negative, and blood culture was positive for Streptococcus viridans. Temperature curve was of an irregular type, with pulse in proportion. On the basis of these findings, a diagosis was made of subacute bacterial endocarditis engrafted upon a mitral stenosis. A few days after admission, the patient was seized with acute pain in the left hypochondrium, accompanied by a rise in temperature. This was attributed to a splenic infarct, and under treatment, symptoms disappeared. Shortly after this, the patient had an attack of pain in the right eye and headache, but an eye examination showed

no abnormalities, and, under treatment, the symptoms subsided. Because of the persistence of the irregular temperature and repeatedly positive blood cultures, in spite of treatment, it was decided to give the patient antistreptococcic serum intravenously. Accordingly, on March 20, 1927, the patient received her first injection of serum. In order to safeguard against the possibility of any untoward serum reaction, in spite of a negative history of hypersensitiveness, preliminary "desensitization" was carried out. Three intramuscular injections of antistreptococcic serum were given at fifteen-minute intervals, the first dose being 0.5 cc., the second 1 cc., and the third 3 cc. No reaction followed any of these injections. Fifteen minutes after the last intramuscular injection, the patient was slowly injected with 15 cc. of the serum intravenously, and except for a slight temperature rise and slight exaggeration of a previously existing headache, no untoward symptoms occurred; certainly no rash, itching, or chills, to suggest a serum reaction. Two days later there was slight improvement in the patient's condition, with slight temperature reduction. On March 24, 1927, 30 cc. of serum were given intravenously, and on the following day, 50 cc. intravenously. Except for slight temperature rise after each injection, no untoward symptoms occurred.

On March 28, 1927, eight days after the first serum injection, the patient developed a mild serum sickness, with pain and burning sensation over the entire body, general weakness, and a moderate edema of the face, especially about the eye, these symptoms disappearing completely in twenty-four hours. Following this, the temperature came down to normal, and the patient improved sufficiently to be walking about the ward.

On April 17, because of the persistence of the positive blood culture, it was deemed advisable to give the patient another injection of serum. Since twenty-three days had elapsed after her last injection, it was realized that an injection at this time might result in an untoward reaction, which it was thought could be prevented by "desensitization." Accordingly, an attempt at "desensitization," similar to that advised by Besredka in guinea pigs, was carried out. The patient was given at half-hour intervals the following doses of antistreptococcic serum intramuscularly: first dose, 0.1 cc. diluted to 1 cc. with normal saline; second dose, 0.5 cc. serum diluted to 1 cc. with normal saline; third dose, 2 cc. undiluted; fourth dose, 5 cc. undiluted. There was no reaction, either locally or generally, following any of these injections. A half hour following the fourth intramuscular dose, the patient was given serum intravenously, the serum being injected very slowly from a syringe. When almost 10 cc. had been given, the patient suddenly sat up, complained of general burning all over the body, and immediately fell back in deep collapse, with marked cyanosis, irregular pulse and slow breathing, which was not of an asthmatic type. The injection had been discontinued at the onset of the attack, and stimulation of various kinds given, but, in spite of these measures, death ensued. Permission for necropsy was unfortunately refused.

Before discussing the unusual features of this case, it is necessary to determine the nature of the reaction. It may be pointed out that one of the outstanding symptoms of the fatal reaction was one that had been prominent in the serum reaction which the patient had suffered three weeks previously, namely, the burning sensation over the entire body. In view of this similarity in the symptoms, there can be no doubt that the fatal attack was a serum reaction in the sense of von Pirquet and Schick.

Serum reactions in general have been classified by von Pirquet

and Schick[6] into three types: Normal, accelerated and immediate. The "normal serum reaction," or serum sickness, as it is commonly known, is that coming on after a latent or incubation period of six to fifteen days, following a primary serum injection or series of injections. Such a reaction did occur in our patient eight days after the initial injection, but it was of the usual mild character. An "accelerated serum reaction" is one characterized by a marked shortening of the latent period to less than three days, and is usually more severe. The term "immediate reaction" was applied originally to those reactions occurring within the first twenty-four-hour period following the injection, but in Goodall's[7] experience, most of these occurred within the first six hours. Essentially, it is a type of accelerated reaction with an unusually short latent period, so that the term "accelerated reaction" can be applied to both. Such reactions seem particularly prone to follow reinjections* of serum (Goodall), and they are apt to be more severe in persons who have previously had a normal reaction following the primary injection. This type of reaction may come on some hours after the reinjection, or within a few minutes. Thus, in a case to be reported by Dr. Janet Travell[8] of the New York Hospital, the first symptoms of a serum reaction following the subcutaneous injection of about 1.5 cc. of tetanus antitoxin were noticed within two to three minutes, and the height of severity was attained within two and a half hours. In this instance, the primary injection had been given one year previously. The interval of time preceding the reinjection seems to have little bearing on the character or time of onset of the reaction, as long as it is after the usual latent period for serum disease. In a case reported by Waugh,[9] the primary injection had been given ten years prior to the reinjection, and yet fatality followed the latter.

The immediate serum reaction following reinjection of serum must be distinguished from the atopic serum reaction which follows the first injection of serum, more particularly in horse asthmatics. The fact that our patient tolerated the primary intravenous injection of from 15 to 50 cc. of the serum is ample evidence of the absence of natural or atopic hypersensitiveness to the serum. As a contrast, reinjection of a total of 8 cc. intramuscularly and 10 cc. intravenously produced symptoms of generalized burning and collapse. These symptoms were similar to those which the patient had during her first serum reaction, but, of course, much more severe. One cannot exclude the possibility that such a severe reaction in a patient with a subacute inflammatory heart condition is more apt to result fatally than in normal individuals; nevertheless, it would seem, from these facts, that death here was due primarily to a severe accelerated serum reaction.

* The term "reinjection" used in this paper applies to the injection given *after* the usual latent period for the normal reaction, as contrasted with a primary injection, referring to that given *before* the onset of the normal reaction.

Just why certain individuals should become more prone to develop severe serum reactions upon reinjections, is not at all understood. We do know that, in normal individuals, a large proportion will develop serum sickness after primary serum injections, the proportion being much higher with certain kinds of sera (about 90 per cent in the case of antistreptococcic or antipneumococcic sera). We also have evidence that a goodly proportion (74 per cent in Goodall's series) of these, upon reinjection, are prone to develop accelerated reactions which, fortunately, in only a very small percentage of cases will be severe enough to result fatally. The nature of these reactions or the mechanism involved is, however, still an unsolved problem. The fact that such individuals seem artificially to have been rendered sensitive to foreign serum and that, as in our patient, death resulted from a reinjection, would seem to be in favor of the anaphylactic character of such reactions. However, in this particular instance, no attempt was made to obtain any evidence, such as skin test, passive transfer, or demonstration of anaphylactic antibodies in the patient's serum, all of which would have rendered more certain the possibility that the reaction was the result of an antibody-antigen combination. As has been previously stated, the evidence in favor of the anaphylactic character of these reactions is far from conclusive, and considerable difference of opinion exists on these questions. In view of this, it would seem advisable, until more definite evidence is obtained, to restrict the term "anaphylaxis" to that to which it was originally applied, namely, to the reaction occurring in the lower animal, and to apply the noncommittal term "serum reaction," either normal or accelerated, to reactions following the administration of foreign sera in human beings.

Such an experience as that recorded above brings out several important facts which should guide us in our future use of serum therapeutically. In the first place, it would seem, in the light of our experience, that, if reinjections of serum are to be undertaken, one must remember that such reactions are fraught with the danger of what might preferably be termed an "accelerated serum reaction," and, since most of the patients to whom such serum is to be given are quite sick, such reactions may be fatal.

Therefore, under such circumstances, one must weigh carefully the possible dangers mentioned above, on the one hand, and the absolute indication and therapeutic value on the other. Should such an injection be deemed necessary—since, in our patient, 8 cc. of serum were given intramuscularly in a two-and a-half-hour period, without any untoward reaction—it would seem that, in some cases, subcutaneous administration of smaller quantities at frequent intervals might be given without danger of fatality. Certainly, intravenous administration should never be attempted unless urgently indicated, as it is more likely to result in fatality, and, even with

subcutaneous injection, one should be on the alert for any signs of an untoward reaction, the injection being immediately discontinued should they appear.

Finally, this case demonstrates a third instance of failure of attempts at so-called "desensitization," in what might be considered a fair trial of its use. Two instances have been previously recorded, the first reported by Koch[10] in 1915, in which 5 cc. of serum subcutaneously, five hours before the final injection, failed completely to protect the patient. In the second case, reported by Blankenhorn[11] in 1925, seven doses of serum, beginning with 4 minims and ending with 5 cc., were given subcutaneously at two-hour intervals, and yet, in spite of this, 5 cc. of serum, intravenously given thereafter, produced a severe and almost fatal reaction. In our patient, 8 cc. of serum given intramuscularly in a two-and a-half-hour period should have been sufficient to protect the patient against less than 10 cc. intravenously, if true desensitization, as practised in the lower animals, is assumed to occur in the human.

These failures of desensitization may be considered as additional evidence[12] arguing against the anaphylactic character of serum reactions; but the number of cases is too small to be conclusive. They would certainly seem to indicate, however, that such methods of "desensitization" in the human are probably of little or no value in the prevention of serum reactions. The reasons for such failures is rather difficult of explanation, at least from our present knowledge of this subject; however, investigation into possible factors is at present being conducted and will form the basis, it is hoped, of a future report on this subject.

Summary. An unusual and fortunately rare type of serum reaction is recorded in a patient in whom death followed the intravenous reinjection of 10 cc. of antistreptococcic serum, twenty-eight days after a primary injection of 95 cc. of serum and twenty days after a mild serum sickness. Death here was due to a severe accelerated type of serum reaction, and occurred in spite of a preliminary attempt at so-called "desensitization." A review of the literature on serum reactions seems to indicate that severe reactions of the type herein described are more prone to follow reinjections of serum, particularly in persons who have previously had a normal type of serum reaction after their primary injection. This is borne out in the case recorded. In view of this, in considering the reinjection of serum therapeutically in any patient, after the usual incubation period for serum sickness has passed, one must remember that such an injection is fraught with some danger of a severe serum reaction or even death. If such an injection must be given, subcutaneous administration is preferable because less dangerous. Furthermore, in such instances, one cannot place any reliance on the methods of so-called "desensitization" in protecting the patient against a serum reaction, since such methods have been copied from similar

methods used in the lower animals, without any definite proof that they are effective in the human; on the contrary, this record constitutes the third published clinical failure of these methods.

Finally, since the question as to the anaphylactic character of serum reaction is still a mooted one, it would seem advisable, for the present, to restrict the term "anaphlyaxis" to the antigen-antibody reaction occurring in the lower animals, and to apply the noncommittal term "serum reaction," either normal or accelerated, to reactions following the administration of foreign sera in human beings.

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ENCAPSULATED PERICARDIAL EFFUSION.

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Encapsulated pericardial effusion is a condition to which little reference is made in clinical literature. Even mention of it as a necropsy finding is scant, a notable exception being Delafield.

In marked contrast to pleural effusions, which are often encapsulated, it rarely happens that fluid in the pericardial sac is walled off by adhesions. It is true that the exudate in pericarditis has an abundance of fibrin, which, according to all observers has a great tendency to become adherent and to organize; nevertheless, the constant movement of the heart, which is apt to be tumultuous in those conditions associated with pericarditis, probably prevents the formation of encapsulating adhesions during the early stage of pericardial effusion.

Yet it would be strange if pericardial effusions did not occasionally exhibit the same exception to rule which we observe in other clinical

conditions. Such, in fact, is the case, as will be illustrated in the cases of encapsulated pericardial effusion which we report herewith.

We may assume, by analogy from the pleura, that pericardial adhesions are most apt to form in those situations in which the movements of the heart are least energetic, namely, in the region of the great vessels and along the right border at the site of the right auricle. These also happen to be the locations in which, according to most authors, effusions early develop. The observations of Roth[1] and Ebstein[2] and the experiments of Aperti and Figaroli[3] have shown that effusions first collect in the cardiohepatic angle. The region of the great vessels, especially on the left side, is also the site of early accumulation of pericardial exudate, particularly in the horizontal position. It is to be expected, therefore, that when adhesion of the pericardial membranes occurs at either of these sites, fluid will be prevented from collecting there and it will be found at the alternate site. The area of heart dullness will then exhibit a disproportionate enlargement either to the right or to the left and upward.

We wish to record in brief the following 4 cases of encapsulated pericardial effusion.

Report of Cases. CASE I.—I. S., July 10, 1924, aged twenty-eight years, has had sorethroat several times in past year. Eighteen days ago polyarticular rheumatism developed and this has continued to present. Last night he had dyspnea.

Physical examination shows moderate cyanosis, heart enlarged, especially to right; cardiohepatic angle dull; sounds diminished; soft systolic murmur at the apex. White blood cells are 15,700; polymorphonuclears, 80 per cent; temperature, 103° F.; pulse, 140.

July 11: Roentgenogram shows an unusual configuration of the heart: The right border is at the midclavicular line; the left border in normal position.

July 12: Right border of heart has moved out to 8 cm. in the fourth space and 9.5 cm. in the fifth space.

July 13: Patient is more comfortable: Temperature, 98° F.; pulse, 112. Right border of heart has receded to 7 cm. in the fifth space. A to-and-fro leathery friction is heard over midsternum. No dyspnea.

July 16: Roentgenogram shows a further recession of the right border, almost to the normal position.

July 20: Right border 3.5 cm. to right in fourth space. No friction murmur.

The patient was observed again October 28 and physical and Roentgen ray examination showed heart normal in size and shape. There was a soft systolic murmur at apex.

Comment on Case I. It will be noted that physical examination on July 10 showed an enlargement only to the right. The cardiohepatic angle was obliterated. On July 12, the right border moved out 9.5 cm. in the fifth interspace. The Roentgen examination on July 11 showed a marked increase of the heart shadow to the right (Fig. 1). The left border was normal in position. On July 13,

corresponding to a recession of the heart border and improvement in the patient, the Roentgen ray examination showed the right border had somewhat receded (Fig. 2). A friction murmur was then heard over the midsternum. It should be noted that the left border of the heart was normal in position throughout the illness. A Roentgenogram on July 16 (Fig. 3), showed the right border in normal position.

CASE II.—J. Z., October 22, 1924, aged eleven and a half years, has had frequent sorethroats, rheumatism four months ago complicated by heart disease, and since then mild rheumatism. For three days he had had cough and fever.

Physical examination showed him to be acutely ill, moderately dyspneic, and with pneumonia right lower lobe. Heart: Right border 3 cm. to right in fifth space. Left border 10½ cm. in fifth space. Mitral insufficiency.

October 25: Roentgenogram shows a normal configuration of the heart.

October 31: In the first and second space to left of sternum, a low-pitched friction sound is heard.

November 2: The heart borders are:

Space.	Right.	Left.
II	1½ cm.	2 cm.
III	2 cm.	3 cm.
IV	3 cm.	5½ cm.
V	5 cm.	8½ cm.

Temperature between 100° and 102° F.

November 5: Heart borders:

Space.	Right.	Left.
II	4½ cm.	2½ cm.
III	5½ cm.	4½ cm.
IV	10½ cm.	7½ cm.
V	11 cm.	8 cm.

November 9: Roentgenogram shows pneumonia, right lower lobe; heart enlarged to the right midclavicular line.

November 10: Heart borders:

Space.	Right.	Left.
II	2½ cm.	2 cm.
III	3½ cm.	3 cm.
IV	5 cm.	6½ cm.
V	7 cm.	8½ cm.

November 18: Temperature is normal. The right border of the heart is close to the sternum.

December 2: Roentgenogram shows slight general enlargement of the heart, and recession of the right border.

Comment on Case II. In this case, we were fortunate in observing the patient before the onset of the pericarditis and accordingly could assure ourselves of the normal outline of the heart before the onset of the pericarditis.

On October 31, a friction rub appeared and by November 5 the right border of the heart had extended to 11 cm. from the mid-

sternum in the fifth space, the left border remaining approximately in its normal position. On November 9, the Roentgen ray examination showed unmistakably the increase of the heart shadow to the right due to a local pericardial effusion (Fig. 4). Note that the left border remained fixed in its previous position. On November 18 both the clinical and Roentgen ray examination showed the right border to be normal in position (Fig. 5).

CASE III.—S. P., aged six and a half years, admitted May 21, 1923, eight weeks ago had sorethroat with fever, and was well after three weeks. Two weeks later he developed rheumatism with endocarditis, and since then has been ill with rheumatism and fever.

Physical examination: Heart size:

Space.	Left.
I	2 cm.
II	5 cm.
III	7 cm.
IV	8½ cm.
V	9½ cm.
VI	11 cm.

At apex a friction murmur. White blood cells 15,100; polymorphonuclears, 61 per cent.

May 25: Friction murmur is loudest at xiphoid.

May 30: Friction has disappeared. Temperature is irregular, up to 104° F.

Comment on Case III. This case illustrates an encapsulation of the effusion to the left of the heart near its base. The physical examination showed a marked increase in the heart dullness in the second left interspace. Note the absence of any shadow in Rotch's space where the pericardial cavity was presumably obliterated by adhesions (Fig. 6).

CASE IV.—J. B., aged seven years, admitted February 10, 1926, was in the hospital for the first time in November, 1922, when a cardiac lesion was already present. At that time a Roentgenogram showed a moderate enlargement of heart with a mitral shape.

On this admission the patient gives a history of subacute rheumatism off and on since 1922. On the morning of admission he complained of pain over the heart with dyspnea.

Physical examination shows no dyspnea or cyanosis. The heart apex is in the fifth space, 1.5 cm. from the nipple, the right border 2 cm. from the sternum. There is a loud systolic murmur of mitral insufficiency. A friction sound is heard near the nipple.

February 12: Friction sound at the left sternal margin.

February 13: Temperature 102° to 104° F. A loud friction is heard over the precordium.

February 14: Superficial cardiac dullness is much increased; it extends from 2 cm. to right of the sternum, to the left posterior axillary line. A loud friction is heard at the ensiform. There are signs of pulmonary compression at the left base.

February 15: Friction is heard in the third left interspace.

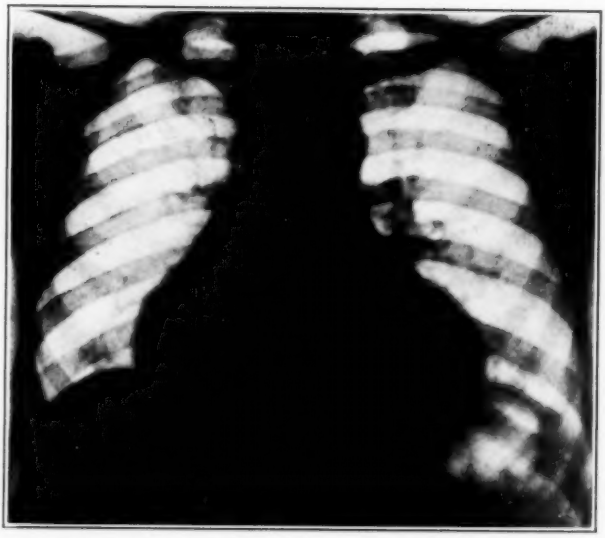

FIG. 1.—Case I (July 11). Marked enlargement of the heart to right due to localized pericardial effusion. Left border in normal position.

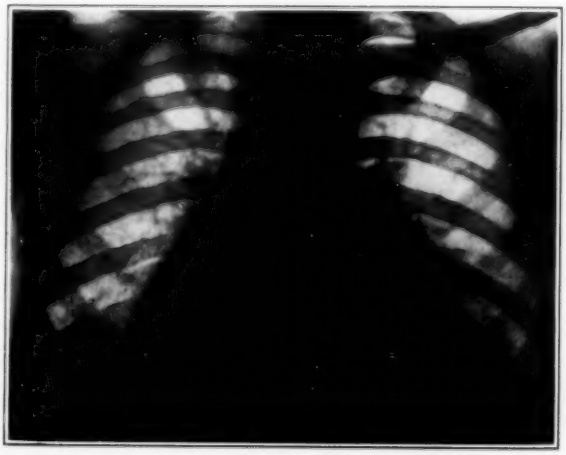

FIG. 2.—Case I (July 13). Two days later, showing recession of right border due to partial resorption of pericardial effusion.

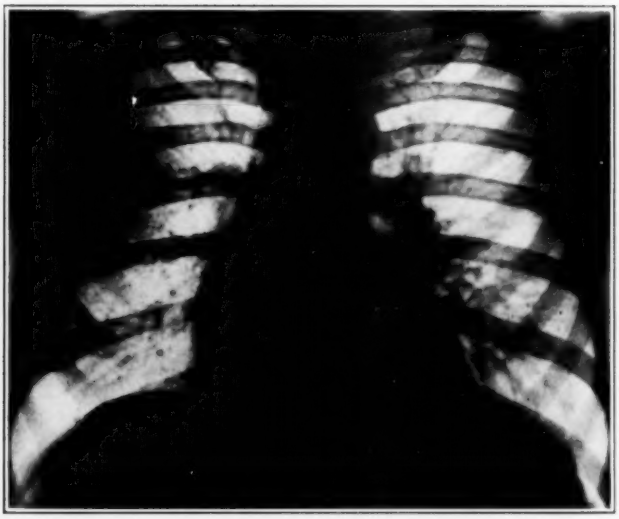

FIG. 3.—Case I (July 16). Three days later, showing normal configuration of heart.

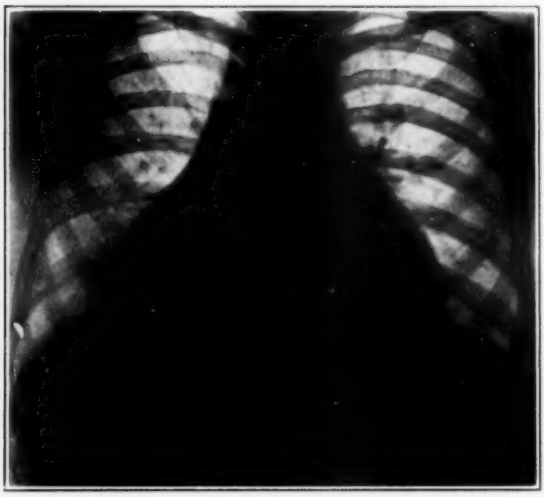

FIG. 4.—Case II (November 9). Enlargement of heart to right due to localized pericardial exudate. Left border normal.

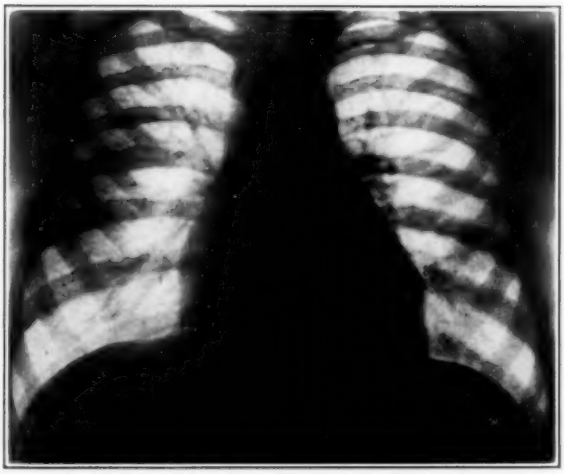

FIG. 5.—Case II (November 18). One week later, complete absorption of exudate. Normal appearance of heart.

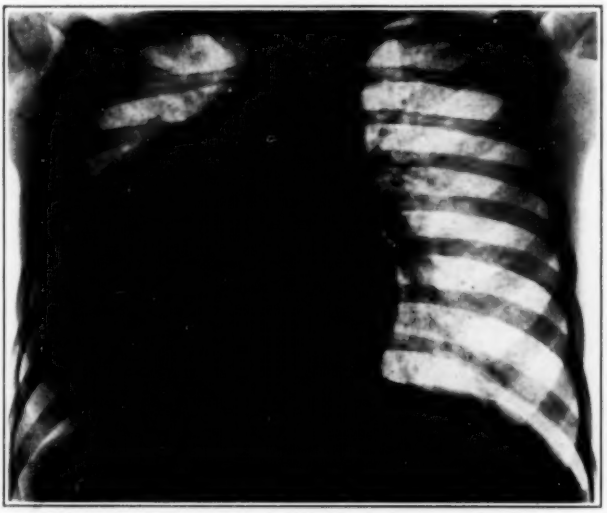

FIG. 6.—Case III.—Pericardial exudate confined to left side.

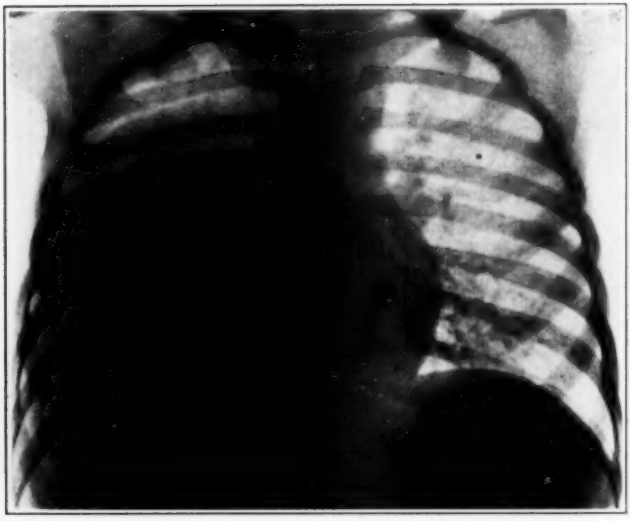

FIG. 7.—Case IV.—Large pericardial effusion limited to left side.

February 16: Roentgenogram shows a marked increase in the cardiac shadow to the left and upward (Fig. 7).

February 23: Fever persists. The pericardial murmur is gone. Dullness extends over the heart to axilla, and up to the third rib. The left chest is resonant and breath sounds are normal.

February 26: Afebrile three days. The apex impulse is strong. Dullness in axilla has disappeared.

May 8: Roentgenogram shows an enlarged mitral heart with no signs of pericarditis.

Comment on Case IV. As in the previous case, the fluid accumulated at the base of the heart and Rotch's space was clear. On admission, the cardiac dullness was 5 cm. from the left of the sternum in the second space and three days later the superficial cardiac dullness had extended to the posterior axillary line (Fig. 7).

Discussion. We have presented 4 cases of rheumatic heart disease in which there was clinical evidence of a fibrinous pericarditis, and in addition, signs of a unilateral enlargement of the heart. Further, in corroboration of the clinical signs, there was in each case a unique change in the configuration of the heart which we have interpreted as a localized pericardial effusion.

The question arises whether these findings, especially the Roentgen ray appearance, permit of any other interpretation. It will at once be suggested that the enlargement of the heart shadow may be due to a cardiac dilatation resulting from valvular disease. This objection can be disposed of with little difficulty. The marked isolated enlargement to the right in Cases I and II is never seen in any form of valvular disease. It is true that the right border of the heart may be found far beyond its normal position in the advanced stages of mitral disease. Under these conditions, however, there is nearly always a coincident enlargement of the heart to the left, which was not present in our cases. In Cases I and II we know that the disease was of very recent origin and in one of them (Case II) the Roentgenogram made before the onset of the pericarditis showed a normal heart. Nor were there any symptoms or physical signs of embarrassment of the circulation as would be associated with a dilatation of the right side of the heart. Under any other assumption than that of a localized pericardial effusion it is not possible to explain consistently with the known facts of the mechanics of cardiac enlargement a rapid enlargement of the heart shadow to the right, as it occurred in these cases.

Finally, the rapid recession of the right border of the heart coincidentally with an improvement in the condition of the patient is, in accordance with clinical experience, more plausibly explained by a resorption of a pericardial exudate than by a decrease in the size of the heart.

The same considerations apply to the 2 cases in which the deformation affected the left border of the heart. Such a configuration

would be unique in valvular lesions as would also its rapid disappearance. In Case III the disease lasted at most eight weeks.

Aside from disease of the heart itself, a localized pericardial effusion must, in exceptional cases, be differentiated from effusions encapsulated in the mesial or mediastinal portion of the pleural cavity. Romberg[4] has pointed out the similarity in the area of dullness of these two conditions and there is no doubt that their Roentgen appearances may closely resemble each other.[5] There are, however, clinical points of distinction. Pericardial effusions are fugitive and are accompanied by a pericardial murmur. Pleural effusions, on the other hand, are more lasting. Finally, a mesial or mediastinal pleural effusion of any size displaces the heart to the opposite side. This is not true of a localized pericardial effusion.

Summary. We would summarize the salient points in the diagnosis of this rare condition as follows:

1. The presence of a pericardial murmur.
2. A rapid increase in the cardiac dullness to the right or to the left infraclavicular region.
3. A unique Roentgen configuration of the heart corresponding to the area of dullness.
4. The rapid change in the contour of the heart which would be inconsistent with other causes for such a change in its configuration.

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POSTURAL HYPOTENSION WITH SYNCOPE: ITS SUCCESSFUL TREATMENT WITH EPHEDRIN.*

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Postural hypotension is the descriptive name given to a syndrome manifested by a small group of apparently healthy persons; the assumption of the upright posture produces sufficient fall in blood pressure to cause marked dizziness and syncope. There are

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also signs and symptoms sufficiently uniform, in the few cases observed and reported, to indicate that this condition is undoubtedly a morbid state. A thorough review of the literature to date reveals but 3 recognized and reported cases. In 1925 Bradbury and Eggleston[1] reported 3 cases of postural hypotension, all exhibiting the following common phenomena: (1) Syncopal attacks on change of posture with a drop of the systolic blood pressure to the shock levels; (2) slow and unchanging pulse rate with marked variation in the blood pressure; (3) anhidrosis; (4) increased distress during the heat of the summer months; (5) slight decrease in basal metabolic rate; (6) signs of slight and indefinite changes in the nervous system; (7) blood urea at upper normal level. Other pertinent signs or symptoms reported in one or more of Bradbury and Eggleston's 3 cases were: (1) Greater excretion of urine during the night than in the daytime; (2) loss of sexual desire and potency; (3) a false general physical appearance of youth in comparison to true age; (4) pallor of skin and mucosa; (5) secondary anemia. The condition, according to these authors, was not amenable to treatment and caused true disability.

It is apparent that the vertigo and syncope observed in postural hypotension must be distinguished from those associated with toxic vertigo, states of exhaustion, the Stokes-Adams syndrome, intracranial lesions, epilepsy and vestibular disease. It is probable that, if the postural blood pressure were determined as a routine whenever dizziness and fainting are complained of, additional cases of this interesting disease might be revealed.

This report is based on 2 cases observed in the hospital and carefully studied from the physiologic standpoint.

Report of Cases. CASE I.—The patient, a construction worker, aged forty-four years, complained chiefly of dizziness and spells of fainting. He was admitted, January 11, 1924. The family history was essentially irrelevant. He had had diphtheria and malarial fever, and three attacks of gonorrhea complicated by arthritis.

In the autumn of 1915 attacks of dizziness and hazy vision first appeared soon after rising in the morning, lasting from one-half hour to one hour and accompanied by watering of the eyes. The attacks increased in severity. Dull lumbar and thoracic distress or pain occasionally complicated them. The patient could relieve the symptoms of haziness and dizziness by lowering his head into the stooping position or lying down. When not in position to do this he would collapse into true syncope for from thirty to sixty seconds, after exhibiting slight muscular twitching. There was no frothing at the mouth or self injury. Any excitement or discussion of his malady was prone to precipitate an attack, although the patient had noticed that the symptoms never arose when he was in a dangerous position, such as working on a ladder or at a height. Since 1920 the patient had lost all sexual power and libido. During the last few years sweating had disappeared from the hands, face and head. In 1922 he complained for two weeks of an attack of dull, gnawing epigastric pain, beginning two hours after meals and lasting until the next meal. The same gastric

symptoms recurred for three weeks in 1923 and again in December, 1923, for two days.

The patient was slightly undernourished. There was no abnormal pigmentation. A marked degree of pyorrhea alveolaris was present. The heart was of normal size on percussion. The abdomen, genitalia, extremities and reflexes were normal. The basal metabolic rate averaged −7 on four determinations. Roentgenologic examination revealed a small gastric ulcer on the lesser curvature of the stomach. Fluoroscopic examination of the heart and lungs was negative. Electrocardiograms were essentially negative both during and after an attack of dizziness and syncope. The blood Wassermann test was negative. Hemoglobin was 73 per cent. Erythrocytes numbered 4,500,000 and leukocytes 8700. The blood urea was 48, creatinin 1.7, sugar 16 and calcium 10 mg. for each 100 cc. The urine showed a slight trace of albumin and an occasional hyaline cast with numerous pus cells. The cerebrospinal fluid was normal.

The systolic blood pressure, taken with the patient supine, ranged from 120 to 90 and the diastolic from 92 to 60. Within one minute after standing up, the patient's head dropped, the body swayed, one arm jerked in clonic contractions, the knees soon gave way and he sank to the floor in syncope for from one to two minutes with imperceptible pulse, and practically inaudible heart sounds. As he rose slowly from the supine to the erect position and immediately walked about the symptoms came on more slowly; he walked faster and faster to evade them, with his head held lower and lower until unconsciousness supervened. The blood pressure during these symptoms dropped to 60 systolic and 44 diastolic. The pulse when obtainable during the period of low pressure varied from 80 to 88. Within four and a half minutes after the administration of 7.5 minims of epinephrin subcutaneously, the blood pressure (lying down) rose from 80 systolic and 60 diastolic to 240 and 160 respectively; considerable untoward effects such as palpitation, nervousness and anxiety were exhibited.

The patient was sent home early in 1924 without relief. In August, 1924, he wrote that his physicians had given him "gland" extract by mouth and pituitrin subcutaneously for seven days, but refused to continue treating him in that manner, evidently on account of untoward effects. In March, 1925, he reported by letter that he could scarcely walk or stand for any length of time without getting down on his knees to relieve the symptoms. At this time he was able to do some painting, but was forced to sit down at his work. In February, 1926, he wrote that syncope had not recurred for about a year, but complained of severe pain in the back, although he was employed regularly doing chores on a farm. In October, 1926, he reported that his back would not support him when walking and that there was twitching and pain in the arm. He had taken no medicine for a year and a half.

Comment. In the main aspects this patient presented the characteristic signs of postural hypotension with syncope: Decrease in the blood pressure to shock level with assumption of the erect position, geographic absence of sweating, failure of the pulse rate to vary with the low blood pressure, slight depression of the basal metabolic rate, and signs of slight and indefinite changes in the nervous system. Just as in one of the cases reported by Bradbury and Eggleston, sexual desire and potency had been lost. Blood urea was slightly increased and phenolsulphonephthalein excretion diminished; a gastric ulcer was present. The dull distress in the back, and associated clonic muscular contractions preceding the

syncope were unusual.* In this case the use of epinephrin and pituitrin was evidently of no therapeutic value, especially in view of their untoward effects and difficulty of administration. The freedom from syncope since early in 1925 supports the assumption that partial remissions, after a progressive course, may apparently occur. Since the recent report of more severe distress in the back and arms, and muscular twitching, we have been anxious to study this case further, but circumstances thus far have given us no opportunity. The history of malaria and gonorrheal attacks should be borne in mind in connection with Case II.

CASE II.—The patient, a married man, aged forty-one years, came to the Mayo Clinic complaining of weakness and faintness. The family history was essentially negative. The marital history revealed no pregnancies or miscarriages. He had had malaria in 1909 and gonorrheal urethritis in 1915. Since 1910 he had been employed as a theater manager, prior to which he had spent seven years as a contortionist and acrobat with a circus.

Thirteen years previously the patient had noticed that practically the whole right side had ceased to perspire. Seven years previously total anhidrosis, involving the whole body surface, had become noticeable. Ever since then he had suffered accentuated sensations of lassitude and oppression during the summer months. For seven years the patient had experienced attacks of weakness, faintness, spots before the eyes and slight vertigo during physical exertion and on sudden change from the supine to the erect posture. Relief from these symptoms could usually be obtained by sitting or lying down, by walking (especially down a flight of stairs), and at times by crossing his legs (scissors fashion). Symptoms were more likely to be provoked by standing still than by any other attitude. He had been so successful in adjusting himself to these threats that actual attacks of syncope were not common. Occasionally none of these remedial measures would avail him and he would pass into true syncope for from one to two minutes without convulsive phenomena or self injury. Nocturia, three to six times a night, with marked excess of nocturnal over diurnal urine was also complained of. Chronic constipation and total loss of sexual desire and potency had developed during the last seven years.

The patient was excellently developed and well nourished. He appeared to be ten years younger than his age. The skin was dry but soft. No abnormal pigmentation was demonstrable. The teeth had all been extracted and dental plates were worn. All other physical signs were negative save for moderate pallor of his skin and mucosa and mild prostatitis. Lying down, the systolic blood pressure was 120 and the diastolic 90; immediately on standing, it fell to 58 systolic and 40 diastolic. Neurologic examination revealed no organic lesion to account for the anhidrosis and evident changes in the sympathetic system, but the patient was classed as being definitely of the anxiety neurosis type.

The pertinent laboratory data were as follows: Blood Wassermann negative; basal metabolic rate, −7; roentgenologic examinations of the chest and urinary and gastrointestinal tracts negative; electrocardiograms negative; a very slight trace of albumin and a slight amount of pus in the urine; blood urea, 26 mg.; mild secondary anemia; blood smear negative for malarial parasites; slight trace of blood in the stool after a meat-free diet.

After the intravenous injection of 1 cc. of phenolsulphonephthalein 80

* The patient explained these twitchings as being voluntary efforts to maintain the erect position.

per cent of the dye in 75 cc. of urine was excreted in two hours when the patient was upright, while 65 per cent of the dye was excreted in 550 cc. of urine while the patient was supine during a similar interval. The blood sugar was 0.07 gm. per cent in both supine and erect positions. Four hours after the ingestion of 1500 cc. of water, while the patient was standing, sitting or walking about, only 145 cc. of urine had been excreted. Repetition of the procedure with the patient lying down resulted in the excretion of 935 cc. in the same period. Electrocardiographic tracings taken in the supine and erect positions showed no significant changes.

Hypodermic injections of $\frac{1}{60}$ gr. atropin sulphate had no effect on the pulse rate, while the same dose administered to a normal person resulted in a rise of the pulse rate from 76 to 146 within one hour. One-tenth grain pilocarpin, administered subcutaneously with cobalt papers distributed over the skin, revealed some secretion of sweat in all areas except on the arms and legs. This demonstrated that the sweat glands of the neck, axillas, chest and abdomen were capable of reacting to stimulation.

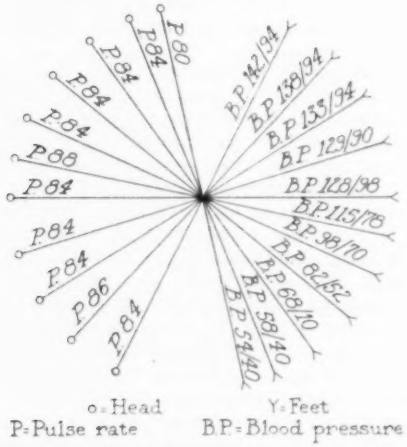

FIG. 1.—Case III. Pulse and blood pressure during progressive changes in the inclination of an adjustable table supporting the patient.

When the patient was erect application of abdominal pressure by means of a pillow and belt decreased the systolic blood pressure 10 mm., but exerted no influence on the diastolic pressure. In the supine position no change in systolic or diastolic pressure resulted from the abdominal pressure.

Change of posture after occlusion of the femoral arteries by means of tourniquets had no effect on the systolic or diastolic blood pressure in the brachial artery.

Fig. 1 shows the changes in blood pressure with passive changes in position. With progressive lowering of the head from almost upright to the horizontal, the blood pressure increased from 54 systolic and 40 diastolic to 128 and 98 respectively without significant changes in the pulse rate. The same procedure, carried out with a normal person as control, revealed a rise of 16 mm. in diastolic blood pressure and a fall of 6 mm. in systolic pressure (Fig. 2). Repetition of the procedure by means of the adjustable table in a severe case of Addison's disease resulted in a rise of blood pressure from 60 systolic and 54 diastolic in the upright position to 78 and 50 respectively in the horizontal position (Fig. 3). In the case of Addison's disease

the same step-like fall was observed with each fractional raising of the head as was manifested to a greater degree in the case of postural hypotension. In the case of postural hypotension further depression of the head to 55 degrees below horizontal provoked a rise of pressure to 142 systolic and

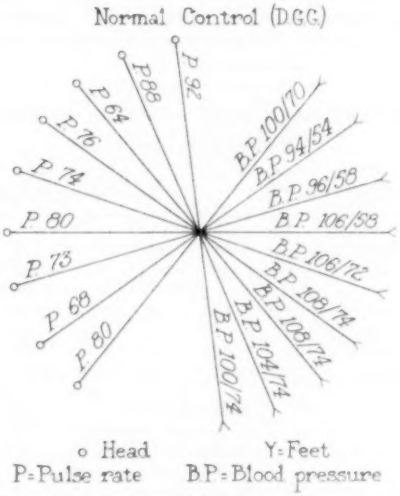

FIG. 2.—Blood pressure and pulse rates with passive change of position in normal subject.

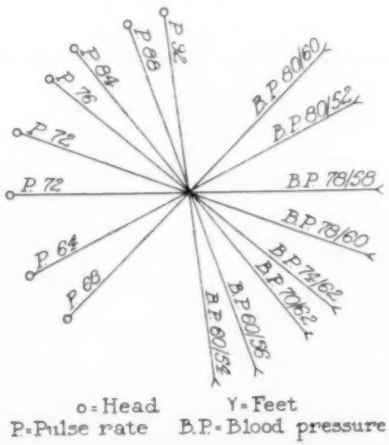

FIG. 3.—Blood pressure and pulse rate in a subject with Addison's disease during passive change of posture.

94 diastolic. None of the other common phenomena of postural hypotension was present.*

Sudden passive change of the patient's position from supine to upright caused an immediate drop of blood pressure from 128 systolic and 98

* Subsequent studies on effects of passive change in posture in Addison's disease show similar reactions in 2 of 8 cases studied.

diastolic to 58 and 48 respectively (Table I). Resumption of the supine posture for one minute brought the blood pressure up to 130 and 98. While in the upright position simple crossing of the thighs (voluntarily) raised the blood pressure from 54 systolic and 40 diastolic to 70 and 50 respectively. The symptoms with change from the supine to the upright position were increased proportionately to the length of time the upright position was maintained. Usually fainting occurred after the third minute (Table II).

TABLE I.—EFFECT OF SUDDEN CHANGE OF POSTURE ON BLOOD PRESSURE (CASE II).

Original posture.			After sudden change of posture.				
Position.	Blood pressure.		Position.	Blood pressure.			
				Immediately.		1 min. later.	
	Systolic.	Diastolic.		Systolic.	Diastolic.	Systolic.	Diastolic.
Horizontal . .	128	98	Upright (passive)	58	48	54	40
Upright . . .	54	40	Horizontal (passive)	108	70	130	98
Upright . . .	54	40	Crossing of thighs (voluntary)	70	50		
Upright, with thighs crossed	70	50	Thighs uncrossed (voluntary); patient upright	50	40		

TABLE II.—SYMPTOMS WITH CHANGES IN POSTURE (CASE II).

Posture.	Time.	Pulse.	Blood pressure.		Symptoms.
			Systolic.	Diastolic.	
Recumbent .	.....	76	128	98	Feels well; no symptoms.
Standing .	Immediately	78	60	40	Mild vertigo, faintness, dimness of vision, weakness.
Standing .	For one minute	76	54	34	Extreme faintness and weakness; body begins to sway.
Standing .	For two minutes	76	40	?	Syncope; falls on the bed.

Following the administration of 4.5 minims (0.3 cc.) of 1 to 1000 epinephrin, while the patient was supine, the pulse rate increased from 84 to 104 within ten minutes (Table III). The systolic blood pressure remained unchanged while the diastolic blood pressure decreased 22 mm. At this time the patient voluntarily assumed the upright position; there was no change in the pulse rate but a sharp reduction of the systolic pressure from 136 to 54 mm. The patient then assumed the recumbent position and the pulse rate increased to 120 as the systolic blood pressure rose to 164 and the diastolic to 70. The usual epinephrin reaction, consisting of palpitation, tremor and nervousness, was present. The patient was again allowed to assume the upright position without change in the pulse rate

but the systolic pressure did not show the previous low level. The diastolic blood pressure, however, remained at its usual level for the upright position.

TABLE III.—EFFECT OF 0.3 CC. OF EPINEPHRIN ON PULSE AND BLOOD PRESSURE (CASE II).

Time.	Position.	Pulse.	Blood pressure.		Symptoms.
			Systolic.	Diastolic.	
3:50 P.M.	Recumbent	84	134	100	Feels fine; no symptoms.
3:55*					
4:05	Recumbent	104	136	78	Slight nervousness.
4:06	Standing	104	54	42	Face pale; slight dizziness.
4:10	Standing (after four minutes of exercise)	104	54	30	Slight pallor; less dizziness.
4:25	Recumbent	120	164	70	Palpitation, tremor and nervousness.
4:26	Standing	120	72	42	No dizziness or weakness.
4:30	Standing (after four minutes of exercise)	120	72	28	No dizziness or weakness.

* 0.3 cc. of epinephrin injected subcutaneously.

TABLE IV.—EFFECTS OF EPHEDRIN: 25 MG. EVERY HOUR FROM 8 A.M. TO 5 P.M. (CASE II).

Posture.	Time.	Pulse.	Blood pressure.		Symptoms.
			Systolic.	Diastolic.	
Recumbent	Forty-five minutes after third dose	112	148	98	Occasional shaky and nervous sensations.
Standing	Immediately	112	120	90	Feels fine.
Standing	For one minute	112	106	68	Feels fine.
Standing	For two minutes	112	100	64	Feels fine.
Standing	For three minutes	112	100	68	Feels fine.
Standing	For ten minutes	112	100	68	Feels fine.
Walking*	Immediately	112	72	40	Feels very slight weakness.
Walking†	Immediately	112	100	58	Feels fine.
Recumbent	Immediately	112	184	118	Slight tremor and slight palpitation.
Recumbent	For four minutes	112	168	110	Less tremor and less palpitation.
Recumbent	For six minutes	112	154	100	Occasional tremor and occasional palpitation.
Recumbent	For eight minutes	112	152	96	Occasional tremor and occasional palpitation.
Recumbent	For ten minutes	112	148	98	Occasional tremor and occasional palpitation.

* Followed by ten exercise movements
† Without exercise movements.

Twenty-five milligrams of ephedrin was given by mouth, hourly, for nine doses. The pulse and blood pressure readings are shown in Table IV. It will be observed that forty-five minutes after the third dose of ephedrin had been given the patient assumed the upright position. The blood pressure gradually decreased in ten minutes from 148 systolic and 98 diastolic to 100 and 68 respectively. The pulse rate had increased to 112, but remained unchanged through this period. The usual effects of the upright position were entirely absent. The patient stated that he felt fine after standing for ten minutes. Walking, followed by a short period of stooping exercises, showed a decrease in the blood pressure to 72 systolic and 40 diastolic after which he complained of slight weakness. The walking experiment was then repeated without the stooping exercises and the blood pressure remained at 100 systolic and 58 diastolic, with no resultant untoward symptoms. The patient was then allowed to lie down and his blood pressure immediately increased to 184 systolic and 118 diastolic. At the end of ten minutes of recumbency the blood pressure was 148 systolic and 98 diastolic and but mild tremor and palpitation were experienced. Ephedrin in dosages of 50 mg. three times a day showed that the blood pressure was 140 systolic and 100 diastolic one hour after the third dose. When the upright position was assumed the blood pressure showed a sharp drop to 54 systolic and 36 diastolic, at which time dizziness and a tendency to sway were noticed. Exercise produced a slight rise in the pulse rate without changes in the blood pressure, and the patient remained practically free from symptoms.

Comment. This patient exhibited the characteristic symptoms and signs as illustrated in the cases previously reported. The assumption of the upright position caused a drop of the systolic and diastolic blood pressure to shock level. When this position was maintained for two or three minutes the patient became definitely pale and would fall. The absence of normal pulse response to this sharp change in blood pressure was most striking. This ability to produce a shock level of blood pressure at will offered an excellent opportunity to determine the variations in certain functions of the kidney. It was found that excretion of phenolsulphonephthalein was greater in the upright position with the low blood pressure than in the supine position under conditions of higher blood pressure; the amount of urine excreted was definitely augmented. This observation was not confirmed. The nocturia, of which this patient complained, was adequately explained by the effect of position on the excretion of water. Four hours after the ingestion of 1500 cc. of water, with the patient in the upright or sitting position, approximately 10 per cent of this amount was excreted. In contrast to this, more than 60 per cent of the water was excreted when the patient was supine. These experiments give indication that the excretion of dye is not affected by blood pressure while the excretion of water is directly influenced by it.

It was noted that, following the injection of epinephrin, the pulse rate increased, while with atropin no change in the pulse occurred. There was no increase of blood pressure with epinephrin while the patient maintained the supine position. Following a period of

standing the pulse rate further increased to 120 and the systolic blood pressure increased, but the diastolic pressure remained as it had been when the patient was lying down. The rise in the systolic pressure was undoubtedly due to the increase in pulse rate. The diastolic blood pressure was not significantly changed by this drug. Ephedrin was most beneficial when given in hourly doses. The pulse rate was increased and maintained. The diastolic pressure was materially increased in contradistinction to that observed with epinephrin.

The patient was dismissed with instructions to take 25 mg. of ephedrin each hour during the period which would best fit his occupational needs. In a letter received two months later he stated he was able to walk any distance and climb stairs; he had been taking 25 mg. of ephedrin five times a day. A second communication, of August 5, 1927, states that he is improving a great deal, is back at work, and suffers from distress only during very hot days. The blood pressure taken by his local physician proved to be: Lying down, 150 systolic and 100 diastolic, and standing, 120 to 80. He has changed the dosage of ephedrin to two or three capsules of 50 mg. each day, and this is apparently sufficient to maintain efficiency in the upright position.

Discussion. The normal physiologic responses of the circulatory system to changes in posture have been carefully studied. Hill and Barnard[7] conclude from animal experiments that, given an intact vasomotor tone, the splanchnic area forms a resistance box for the circulation which minimizes the effect of gravity. They found in dogs, after the vasomotor tone had been destroyed by section of the splanchnic nerves, that the circulation could be maintained by increased expiratory compressions of the abdomen and inspiratory thoracic suctions. These synchronous actions oppose the outflow of blood into the splanchnic vessels and maintain the intake of blood to the heart. They conclude that in man (on assumption of the erect posture) a deficient vasomotor tone with an atonic abdominal wall or patulous abdomen leads to deficient circulation and consequent anemia of the brain. Compression of the abdomen opposes the effect of gravity when vasomotor tone fails. In normal subjects on voluntary changing from the supine to the erect position the pulse rises from 6 to 15 beats, according to Falconer,[5] Graves,[6] Schneider and Truesdale[11] and others. Turner[13] found an approximate rise of 19 beats after three minutes in the upright posture in twenty-four apparently normal subjects undergoing voluntary change. With passive change from supine to erect, the average rise in pulse rate was 10 beats in Mortensen's[9] series of 90 normal women.

The blood pressure variations with change in posture were early described by Crampton,[4] who interpreted these phenomena as evidence of the vasomotor status, especially as related to the splanch-

nic vessels. Mortensen,[9] however, became convinced that the rise in the systolic blood pressure with voluntary postural change was not due to vasomotor tone, but ascribed this to myocardial response to the effect of gravity and to the muscular activity coincident with voluntary change of position. That muscular activity has some definite bearing on postural rise of systolic blood pressure is borne out in the average mean rise of 2.3 mm. systolic blood pressure found by Schneider and Truesdale in their series of 2000 normals after voluntary change from the supine to the erect position. In contrast to this, is Mortensen's series of 90 normal women, who when passively changed from the supine to the erect posture, manifested an average mean fall of 4 mm. in systolic blood pressure. The mean values for the diastolic pressure with passive or active postural change have proved to be essentially the same since both Mortensen's and Schneider and Truesdale's observations revealed a rise of approximately 8 mm. in diastolic blood pressure. Sewall[12] holds that the maintenance of adequate diastolic pressure with change of posture is a measure of peripheral resistance, which is regulated by vasomotor tone.

Abnormal responses to changes in posture have been studied by Turner, who found that apparently normal persons exhibiting symptoms of dizziness and fainting on voluntary maintenance of the stationary erect posture for periods of fifteen minutes showed excessive loss of circulatory minute volume and either progressive rise of diastolic pressure to approximate systolic level or fall of both systolic and diastolic pressure sufficient to cause anemia of the brain. Abnormal fall in systolic blood pressure alone may occur in man on passive change from the supine to the erect posture when the myocardium is functionally incapable of responding to the increased strain on the circulation exerted by gravity. It is in cases of myocardial degeneration that this condition is mostly found. Abnormal fall of diastolic blood pressure alone in man during or after postural change evidently could occur only when deficient vasomotor tone is uncompensated by efficient abdominal and thoracic muscular action which would result in splanchnic congestion of the circulation, even though the myocardium were functionally intact.

An abnormal decrease in both systolic and diastolic blood pressure during or following postural change is found in some cases of Addison's disease, and in some cases of anemia of such severity as to interfere with adequate myocardial function, and sufficient to preclude circulatory efficiency, even though the vasomotor system might still be normal.

True postural hypotension with syncope must be regarded as a definite clinical entity, characterized by its occurrence in those whose health is otherwise good, and the absence of a known cause. The abnormal response to postural change is evidenced by a sharp

fall of the systolic and diastolic blood pressure on the assumption of the erect posture to a level sufficiently low to produce syncope. The vasomotor regulatory mechanism capable of compensating the effects of gravity is greatly impaired. The usual response of the vagus nerve to variations in blood pressure is absent. Other disturbances that may be present are anhidrosis, diminution of basal metabolic rate, signs of slight and indefinite changes in the central nervous system and elevation of blood urea to the upper limit of normal. In 2 of the 5 reported cases there was a history of malarial fever and gonorrheal arthritis previous to onset, more urine was passed during the night than in the daytime, sexual desire and potency were lost, the physical appearance gave a false impression of youth, the skin and mucosa were pale and mild secondary anemia was present.

Addison's disease is excluded by the absence of pigmentation and extreme asthenia, its nonprogressive course and absence of tuberculosis. Hypochromaffinism exhibits congenital inferiority not found in postural hypotension. A cardiac basis is easily eliminated by clinical and electrocardiographic studies during the attack. Epilepsy may be erroneously diagnosed, but the exact relationship of syncope to posture and variations in the blood pressure excludes it. Hysteria must be considered in the differential diagnosis. In Case I the patient was able to control the symptoms under exacting circumstances: He continued to work on heights at his regular occupation without ever fainting or becoming so giddy as to risk his life. In Case II the syndrome was initiated by unilateral anhidrosis which ultimately affected the whole body. Moreover, the widespread involvement of two systems innervated by the sympathetic nervous system suggests a profound disturbance in the emotional activities that influence this system. The loss of libido and history of gonorrhea in both cases provide an adequate explanation of such disturbance of emotions. On the other hand, the failure of pilocarpin to induce sweating in certain areas is an argument in favor of an organic basis.

The high incidence of impotence and loss of libido, along with the history of gonorrhea in 2 of the 5 now reported cases of true postural hypotension with syncope, offers some grounds for an endocrine basis in the production of this disease, especially in view of the work of Wheelon and Shipley.[14] These investigators demonstrated that castration of dogs caused 50 per cent decrease in vasomotor response to nicotine, and ten days after the successful implantation of testicular grafts their vasomotor response to nicotine recovered to 77 per cent of their average normal before castration. The blood pressure in each case fell after castration, the average in all 20 dogs being 5.8 per cent. The testicular grafts raised the average blood pressure approximately 2 per cent in all the experimental animals. Both systolic and diastolic blood pres-

sure shared in these reactions. In view of these observations, it is conceivable that testicular degeneration from gonorrheal or other cause might theoretically be considered as a possible etiologic factor in postural hypotension with syncope. On account of the absence of sharp or decisive variation in the blood pressures in experimental castration, this work is far from settling this controversial question.

The interpretation of the fundamental disturbance in these cases clearly indicates that this condition is a disturbance entity of the autonomic nervous system affecting both the sympathetic and parasympathetic divisions. The major manifestation of the disturbance of the sympathetic system concerns itself with the diminished vasomotor response in the splanchnic vessels to shifts in the blood mass. This diminished vasoconstriction of the splanchnic vessels on assumption of the upright position allows the blood to fall into the abdominal areas to the embarrassment of the circulation to the brain and possibly to the kidneys. The response of the accelerator fibers of the heart to epinephrin and ephedrin is maintained. The parasympathetic disturbance is evidenced by the diminished or absent response of the vagus to changes in the blood pressure and to atropin. The disturbance of the sweating mechanism indicates further involvement of the sympathetic. The response of sweating to pilocarpin was of uneven distribution, although symmetrical. The theoretical site of the disturbance in this disease, on the basis of these observations, could be either central or peripheral. A lesion of the cerebellar and medullary blood vessels could theoretically produce hypotension, vertigo and anhidrosis. There were no definite manifestations of organic disease of the central nervous system to substantiate this conception. A central disturbance based on abnormal emotional reaction is not ruled out. We would agree with Bradbury and Eggleston, that the evidence at hand indicates that the major disturbance manifests itself in the myoneural structures. We do not believe this is a true paralysis but a condition of hypotonia or impairment, and may be secondary to a more fundamental or primary disturbance.

The use of ephedrin has thrown additional light on this disease. The pharmacologic effects of this drug have been investigated by Chen and his associates.[2 3] They have shown that its effects are qualitatively identical with those of epinephrin. In chemical constitution it varies from epinephrin by the absence of two hydroxyl groups attached to the benzene ring in the latter. These two adjacent groups allow rapid destruction of the molecule which explains the transitory action of epinephrin. The benzene ring in ephedrin is unsubstituted and the molecule is much more stable than epinephrin. Miller,[8] and Rowntree and Brown[10] have studied the effects of this drug in cases of hypotension and Addison's disease. They were able to demonstrate that the blood pressure could be definitely increased without significant change in the symptoms.

From the use of this drug in postural hypotension we are inclined to believe that it has a specific pharmacologic effect in this disease by stimulating the myoneural structures of the vasomotor nerves. No analogous effect was noted on the nerves of the sweat glands after the use of this drug. The blood pressure is definitely maintained by small intermittent doses when given orally. The splanchnic vessels maintain a degree of vasoconstriction sufficient to offset the effects of gravity on the blood mass.

The superiority of ephedrin to epinephrin in increasing the blood pressure in this disease is clear. The advantage of oral administration is most important. We are of the opinion that epinephrin produces similar effects, which are, however, too transitory to have clinical application.

Summary. Postural hypotension with syncope, though only observed in 3 cases before the 2 here reported, probably represents a distinct clinical syndrome characterized by reduction of the systolic and diastolic pressures to shock levels on the assumption of the upright posture. The essential disturbance in this disease is the lack of resistance in the splanchnic vessels to shifts in the blood mass and absent or diminished vagus regulation of the heart rate to changes in the blood pressure. The opinion is advanced that this disease represents an hypotonic state of the myoneural structures of the sympathetic and parasympathetic nervous system of unknown origin. The successful treatment by ephedrin in one case allows hope that this drug exercises a specific alleviative effect on the disease.

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CERTAIN ADVANTAGES OF TOTAL THYROIDECTOMY IN SELECTED CASES OF THYROTOXICOSIS OF THE EXOPHTHALMIC TYPE.

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It has been our opportunity to observe for a number of years a large number of patients who had been treated by the usual surgical measures for (severe) thyrotoxicosis of the exophthalmic type.

We could not but recognize: (1) That the return to health of many of them was decidedly incomplete; (2) that quite a number of them relapsed, and this in spite of good medical care.

It also impressed us: (1) That the less of the gland that was left by the surgeon, the better did the patient ultimately become; (2) and the less apt were they to experience a relapse. Further we gradually realized that the less of the gland that was left: (*a*) The less was the postoperative reaction; (*b*) the shorter was the postoperative hospital convalescence; (*c*) and the sooner were the patients able to again resume their old occupations.

We came then to think of the unremoved portion of the gland as a diseased structure in a similar way as we thought, let us say, of an infected tonsil fragment, and it seemed to us probable that the body's needs could be better met by the intake of a proper amount of the extract of a normal gland, than by the perverted secretion of a diseased gland fragment.

With this in mind, we decided to remove from patients suffering from severe thyrotoxicosis of this type all the gland that was surgically removable, and later to administer to them daily the quantity of thyroid extract that appeared to best regulate their metabolic activities.

Twenty-two patients form the basis of this report. All of them had been incapacitated for some time from useful pursuits. Ten of them had been receiving continuous medical care from one to eight years. Eight of the 22 had been given numerous Roentgen ray treatments, 2 of them as many as sixty, and a number of them had been considered poor surgical risks and had come to be regarded as incurable.

Prior to the operation, all were told of what was contemplated and that it would be necessary for them to take daily a certain amount of thyroid extract for the remainder of their lives. No difficulty was experienced in obtaining any patient's consent.

In preparing them for the operative ordeal, relief of dehydration, the taking of a high-caloric diet, and the administration of iodin were regarded as of the greatest importance. Patients exhibiting cardiac decompensation with or without auricular fibrillation were digitalized but apart from this, digitalization was not made a routine procedure.

In only one of them was any preliminary ligation operation performed, for we had not been impressed by the results of such a procedure. Many of them had previously been given Lugol's solution in such a haphazard way, and over such extended periods that it failed to exert its hoped for preoperative and postoperative salutary effect.

The operation, except in the exceptions noted, consisted in removing the thyroid gland as completely as possible, care being taken to prevent injury to the parathyroid bodies, and to the recurrent laryngeal nerves by either shaving the posterior portion of each lateral lobe as close as possible to the capsule, or by stripping the capsule from the posterior surface of the lobe. A careful search was made in every case for an existing pyramidal lobe and this, if found, was removed.

Case Reports. CASE I.—D. H., aged fifty-six years, male, with thyrotoxicosis of the exophthalmic type, had been totally incapacitated for three years. The basal metabolic rate was +43 per cent, the pulse 140 per minute; there was marked nervousness and tremor, shortness of breath and great fatigability.

The patient presented a pitiful appearance with his great nervousness and lack of concentration. His markedly prominent eyes, marked tremor and loss of weight had kept him from his insurance occupation for three years. He had received 40 Roentgen ray treatments and several courses of iodin in addition to the usual medical measures.

A total thyroidectomy was followed by only a slight postoperative reaction and an uneventful convalescence.

The patient's condition demanded thyroid extract, 1 grain daily, three weeks following operation. His basal metabolic rate at that time ranged from −5 per cent to −2 per cent and his pulse rate from 60 to 72 per minute.

At present, two years and three months after operation, this patient has gained 20 pounds in weight, feels perfectly well, has no symptoms and has been at work steadily since two months after his operation. His exophthalmos disappeared promptly, his basal metabolism is normal, his pulse 72 per minute. He requires 1 grain of thyroid extract daily, is calm, full of energy and averages three miles walking daily at his occupation of insurance broker.

CASE II.—W. L. B., aged fifty-four years, male, with thyrotoxicosis of the exophthalmic type, suffered total incapacity for four years. The basal rate was +45 per cent, the pulse 120 per minute; the hands were moist and warm; tremor was present, also marked fatigue and shortness of breath.

This patient's vital capacity was but 50 per cent and shortly before operation on his attempting to work he became seriously ill and lost 40 pounds in weight. Definite cardiac decompensation was present with shortness of breath and swelling of the feet. He had received a total of 50 Roentgen ray treatments and iodin in addition to the usual medical measures. He was digitalized, compensation being partially restored.

RESULTS OF TOTAL THYROIDECTOMY IN 22 CASES OF SEVERE THYROTOXICOSIS.

No.	Age.	Sex.	Exophthalmos.		B. M. R.		Amt. of thyroid removed.	Amt. of extract given daily, gr	General condition.	Remarks.
			Before.	After.	Before.	After.				
1	56	M.	++	0	+43	− 5	Total	1	Excellent	At work since second month; postoperative B. M. R. maintained at normal.
2	54	M.	++	0	+45	−16	Total	2	Excellent	Compensation restored; at work since operation; B. M. R. maintained at normal.
3	29	F.	++	+	+44	−16	Total	3	Good	Does housework; had normal baby; B. M. R. maintained at normal.
4	49	M.	+++	0	+80	?	Pract. total	None	Excellent	Patient at work; has not returned for B. M. R.
5	45	F.	++	0	+60	−21	Total	1	Good	Gained weight; doing strenuous housework; B. M. R. normal.
6	27	M.	+	0	+50	0	Pract. total	2	Good	Returned to studies at college; B. M. R. normal.
7	34	F.	++	0	..	..	Pract. total	None	Excellent	Operated previously—subtotal; second operation practical total; works hard; B. M. R. normal.
8	42	F.	++	+	+30	− 6	Total	1	Excellent	At work as teacher; B. M. R. normal.
9	19	F.	+	0	+42	− 5	Total	1	Good	B. M. R. normal; at work.
10	26	F.	+	0	+61	−14	Total	1	Excellent	Does housework; B. M. R. normal.
11	45	F.	++	0	+69	−12	Total	3	Good	Does housework, feels fine; B. M. R. normal; 2 grains daily.
12	24	F.	+	0	+50	−12	Total	1	Excellent	Had partial thyroidectomy 3 years before; apparently well; B. M R. normal.
13	38	F.	+	0	+73	− 2	Total	1	Good	Back at occupation; feels well; B. M. R. normal.
14	37	F.	+	0	+58	−10	Total	1	Good	Back at occupation; feels well; B. M. R. normal.
15	38	M.	+	..	+74		Total	..	Died	Died suddenly few hours postoperation.
16	21	M.	+++	+	+77	− 4	Total	2	Excellent	Back at work; B. M. R. normal
17	33	F.	+	0	+47	2	Total	2	Excellent	Back at housework; B. M. R. normal.
18	52	M.	+	0	+89	− 2	Total	2	Good	Compensation restored; back at work; B. M. R. normal; pulse, 72; blood-pressure remained high.
19	21	M.	+	0	+34	−29	Total	2	Fair	Compensation restored but signs of autonomic imbalance; fibrillation disappeared; B. M. R. normal.
20	35	M.	+	0	+45	−28	Total	2	Excellent	Back at work; B. M. R. normal.
21	49	F.	++	0	+69	−17	Total	2	Excellent	Back at work; B. M. R. normal; feels fine.
22	32	F.	+++	0	+70	?	Total	2	Excellent	Well; B. M. R. normal.

A total thyroidectomy was followed by no postoperative reaction and by a rapid and uneventful convalescence with disappearance of exophthalmos. The basal rate fell to −16 per cent within four weeks after operation with symptoms of hypothyroidism. Thyroid extract, 2 grains daily, was administered and the rate brought up to normal.

Two years later this patient is feeling well, pulse, 72 per minute, his weight is 170 pounds, a gain of 40 pounds, he has no tremor and he has been at work at his occupation of carpenter since a few months after operation. He receives at present 2 grains of thyroid extract daily. After a hard day's work at carpentering, he walks for exercise, sleeps well and is happy.

Case III.—A. H., aged twenty-nine years, female, married, had a similar condition with total incapacity for six years. The basal rate was +44 per cent, the pulse 116 per minute; there was marked nervousness and tremor, great fatigability and loss of weight.

This patient's nervousness and exophthalmos were extreme as was her fatigability. She had been unable to perform her household duties for six years. She had received Roentgen ray treatments off and on for over a period of three years, iodin, and so forth.

A total thyroidectomy was followed by practically no reaction and an uneventful convalescence.

Following operation, the basal rate fell to −16 per cent after a month. The rate was brought up slowly by means of thyroid extract, the maximum being 3 grains daily. Now the patient feels perfectly well, has gained her normal weight, her pulse rate is 70 per minute, her exophthalmos has disappeared, she feels strong and is able to do her housework, and one month ago gave birth to a healthy 7 pound baby after a perfectly normal pregnancy and labor. Her basal rate is −4 per cent, blood pressure and urine normal. During the pregnancy this patient felt it necessary herself to increase the daily dose of thyroid to 4 grains instead of the usual 2. The basal metabolic rate confirmed the necessity of this as felt subjectively by the patient.

Case IV.—G. C., aged forty-nine years, male, had thyrotoxicosis of the exophthalmic type, with nervousness, fatigability and weakness of a year's duration. This patient did not respond to rest and iodin and (on a consultant's advice) was subjected to ligation of both superior thyroid vessels. This did not appreciably alter his general condition or lower his basal metabolic rate. The latter remained above 80 per cent and his nervousness and motor activity were most marked, he was completely incapacitated from work.

A thyroidectomy was done, but at the request of the consultant physician a portion of the lower left lobe, 1 by 1 cm. in size was left. This operation was followed by no more, if as much, reaction than followed the ligation operation and patient's convalescence was uneventful and prompt.

The basal metabolic rate fell, eleven days following the operation, to 22 per cent. The pulse rate dropped to normal, the nervousness had disappeared as had the exophthalmos and the patient had resumed his occupation within two months. He has failed to report for six months for basal metabolic reading, but sends word he feels well and is hard at work as a contractor.

Case V.—G. T., aged forty-five years, female, married, had thyrotoxicosis of the exophthalmic type, with total incapacity for three years. The basal metabolic rate was +60 per cent, the pulse rate 130 per minute; there were nervousness and tremor, fatigability and loss of weight. She had been given the usual medical treatment.

A total thyroidectomy was followed by a moderate reaction only, and an uneventful convalescence.

A month later her basal metabolic rate was −21 per cent and was readily brought up to normal by thyroid extract. The patient gained rapidly in weight, soon felt and looked like a young woman and became able to carry on rather strenuous housework. At present, two years and nine months after, the pulse is between 68 and 72 per minute, she feels well and is receiving 1 grain of thyroid daily.

CASE VI.—F. S., aged twenty-seven years, male, had thyrotoxicosis of the exophthalmic type. This patient was incapacitated for three years and hospitalized for one year and received 60 Roentgen ray treatments and several courses of iodin during that period. His basal metabolic rate was +50 per cent, fatigability, nervousness, tremor were quite marked. He had lost a large amount of weight.

A total thyroidectomy was followed by no postoperative reaction and an uneventful convalescence.

Within a month, this patient was able to resume his studies at college. His basal metabolic rate was maintained at normal with periodic feedings of thyroid extract, 2 grains daily. When last heard from, a year after the operation, this patient was perfectly well.

CASE VII.—C. W., aged thirty-four years, female, married, had thyrotoxicosis of the exophthalmic type. This patient had been subjected to subtotal thyroidectomy eleven years previously. She did well until two years ago but never lost her exophthalmos completely or her rapid pulse.

During the past two years patient had a return of symptoms. Her exophthalmos had become more marked, she had a pulse rate of 120 to 130 per minute and exhibited nervousness, great fatigability and shortness of breath.

A thyroidectomy was followed by no postoperative reaction and a rapid uneventful convalescence. In this case, at the request of the husband, a piece of thyroid gland approximately 1 by 1 cm. was left.

At present, two years after her operation, she looks and feels well, exercises vigorously, her pulse rate is between 70 and 80 per minute. The exophthalmos has completely disappeared.

This patient passed through two strenuous experiences six months ago. She was operated on for pelvic trouble and later did vigorous work saving personal belongings when her house caught fire. Following these experiences, she reported to see if she had injured herself. She was found to be, apparently, perfectly well.

CASE VIII.—H. W., aged forty-two years, female, single, with thyrotoxicosis of the exophthalmic type, showed markedly prominent eyes, extreme nervousness, tremor, loss of 40 pounds in weight and had been incapacitated partially for the past eight years and completely for the last two.

The lowest point obtained by the basal metabolism after medical treatment, including Roentgen ray, rest and iodin, before coming to our clinic was +30 per cent.

A total thyroidectomy was followed by an uneventful convalescence with no postoperative reaction.

One week after the operation the patient's metabolic rate was −6 per cent. This was brought up to normal with 1 grain of thyroid daily. At present, one year and six months after the operation, she feels well, her pulse is 68 per minute, her nervousness has almost entirely disappeared and she has gained 8 pounds in weight. Her basal rate remains normal, with 1 grain of thyroid extract daily.

CASE IX.—E. W., aged nineteen years, female, single, had thyrotoxicosis of the exophthalmic type. This young woman had been ill for two years.

She showed a marked nervous reaction, moderate exophthalmos, marked tremor with warm, moist palms and was incapacitated.

The basal metabolism was +42 per cent, the pulse varied from 110 to 130 per minute, and she had been treated with the usual medical measures, including Roentgen ray and rest.

A total thyroidectomy was followed by a moderate reaction shown by a postoperative temperature of 101° F. Patient's convalescence was uninterrupted. Her basal metabolism was −5 per cent two weeks after the operation and she was given ½ grain of thyroid extract daily.

Six weeks after operation this patient looked and acted like a different person. Her pulse was 74 per minute, she gained weight, felt well and strong and her exophthalmos had nearly completely disappeared. She showed no tremor and her skin was of normal temperature. At present, sixteen months after operation, her basal rate is normal and she has regained her weight. She takes 1 grain of thyroid extract daily.

Case X.—S. M., aged twenty-six years, female, married, had thyrotoxicosis of the exophthalmic type. The patient had been incapacitated from performing her household duties for about one year. She was nervous, had lost some weight and tired readily. On examination, there was found some prominence of the eyes and stare, tremor and a pulse of 110 per minute. This patient had been a trained nurse previous to her marriage and because of her experience of other patient's cases preferred to be operated on rather than to undergo medical treatment. A total thyroidectomy was done. This was followed by no untoward reaction and her convalescence was uneventful.

Shortly after the operation her basal metabolism was −14 per cent. She was given thyroid extract, 1 grain daily, which restored her basal metabolism to normal.

At present, one year and six months after the operation, the patient is well, feels cheerful, is able to work and has a pulse rate of 70 per minute with a normal basal rate. She requires from 1 to 2 grains of thyroid extract daily.

Case XI.—M. S., aged forty-five years, female, married, with exophthalmic thyrotoxicosis showed marked nervousness, fatigability, loss of weight to 85 pounds and a large thyroid with typical bruits over it. She had a marked tremor and moderate grade of exophthalmos and had been completely incapacitated over a long period.

This patient had had six Roentgen ray treatments but in spite of these and a preliminary rest in bed and iodin she showed a basal rate of +69 per cent and a pulse of 136 per minute.

A total thyroidectomy was followed by an uneventful convalescence and marked immediate improvement.

The basal rate dropped in two weeks to −2 per cent and later to −12 per cent. In spite of the administration of 1 grain of thyroid extract daily, this remained low but on 5 grains daily it was brought up to normal and maintained there.

For a year previous to her operation, this patient had had irregular menstruation. Following the operation during the period in which the basal rate was low she suffered from severe menorrhagia, her hemoglobin going as low as 40 per cent. With the return to a normal basal rate, the periods became regular and painless though inclined to be scanty.

Over a year and three months after operation this patient feels very well, weighs 108 pounds, shows a normal basal rate and a pulse of 88. She still shows some nervousness but is well able to do her work and lead a normal life taking 1 grain of extract daily.

CASE XII.—U. P., tall female, aged twenty-four years, married, with thyrotoxicosis of the exophthalmic type. This patient had had a partial thyroidectomy three years previously and felt well for six months, gaining 40 pounds in weight and showing no nervousness for that period. The nervousness and fatigability accompanied by loss of weight reappeared gradually and six to eight months prior to coming to us had become very marked. When presenting herself she was a thin, very nervous woman with staring eyes, an enlarged left thyroid lobe showing a loud bruit. Her basal rate was +50 per cent; pulse, 120 per minute; weight, 120 pounds. She was markedly nervous and showed an exaggerated tremor. Nausea and vomiting were distressing symptoms. For six months she had been unable to work.

A total thyroidectomy, after a considerable preoperative period of rest and iodin, was done and followed by an uneventful convalescence. Her basal rate dropped in two weeks to −12 per cent and was brought to normal by 2 grains daily of thyroid extract. The pulse dropped to 60 per minute but later, two weeks, came up to 70 per minute and a month later to 76 per minute. Two months later the basal rate was normal, she had gained to 160 pounds, felt perfectly well and showed none of the previous signs.

Her strength was good, she was menstruating regularly and able to work hard. She is now taking 1 grain of thyroid extract daily and is apparently perfectly well, thirteen months after operation.

CASE XIII.—K. P., aged thirty-eight years, female, married, showed extreme nervousness, tremor, moderate exophthalmos and a stare, a moderately large thyroid with characteristic bruits, a basal rate of +73 per cent and a pulse of 120 per minute. Her motor nervousness was so extreme that rest in bed was hardly possible.

After fourteen days of hospitalization with iodin all symptoms diminished considerably and the basal rate dropped to +55 per cent and pulse to 100 per minute.

A total thyroidectomy was followed by an uneventful and rapid convalescence. In four days her stare had practically disappeared, her pulse dropped to 76 per minute and she was quiet and without tremor.

Thirteen months later patient looked and felt well, had a normal basal rate and presented no signs of disease. Her basal rate dropped to −2 per cent. Weight, 138 pounds. Menstruation regular. She takes 1 grain of thyroid extract daily.

CASE XIV.—A. C., aged thirty-seven years, female, married, showed extreme nervousness, diarrhea, moderately prominent eyes, an enlarged thyroid with bruits and an enlarged heart with a loud systolic murmur.

Patient's tremor was marked and she had had her symptoms for eight years. She had noted gland enlargement for a year. Her basal rate was +58 per cent; pulse, 100 per minute; weight, 112 pounds.

She was kept under preliminary medical treatment and her basal rate came down to +32 per cent, accompanied by symptomatic improvement.

A total thyroidectomy was followed by a convalescence complicated by bronchopneumonia symptoms, which persisted for ten days.

Three weeks after operation patient looked and felt well and showed loss of her former symptoms. This patient lives in another state and has been lost track of. When last seen her pulse was 70 per minute. Eye signs had markedly diminished, nervousness and tremor had gone. She felt fine and showed a basal rate of −10 per cent. She took 1 grain of thyroid extract daily.

CASE XV.—C. M., male, aged thirty-eight years, had been invalided for three years with thyrotoxicosis of the exophthalmic type. He had been

refused operation a number of times on account of his enlarged irregular heart fibrillating to a marked degree. Treatment including digitalis and quinidin did not influence this irregularity. His basal rate was +74 per cent in spite of 15 Roentgen ray treatments. His pulse was 100 at the wrist.

After iodinization and digitalization his rate dropped to +25 per cent and his pulse was 80 per minute at the wrist but more rapid at the apex. He felt better.

Total thyroidectomy apparently did not upset this patient and he was returned to the ward in seeming good condition.

However, five hours after operation the patient suddenly expired with symptoms of acute cardiac failure. A postmortem examination was not permitted.

CASE XVI.—O. Y., male, aged twenty-one years, single, had been ill for four years, desperately so for about six months. When first seen he was extraordinarily nervous, rendering rest practically impossible, had lost considerable weight—from 220 to 118 pounds—and perspired profusely. He had a very exaggerated exophthalmos and other eye signs, great tremor, a pulse of 130 per minute and a very large thyroid with large bruits. His blood pressure was 180 systolic, 70 diastolic and basal metabolism +77 per cent.

This patient was kept as quiet as possible for a month and received iodin and high-caloric diet with only moderate improvement. Prior to operation his basal rate was +49 per cent, his weight was up to 160 pounds and pulse down to 102 per minute.

Total thyroidectomy was followed by an uneventful convalescence and an immediate amelioration of symptoms.

When he left the hospital two weeks after operation he had gained weight, pulse was 80 per minute, nervousness greatly diminished, exophthalmos 75 per cent less, he felt fine and showed no tremor. His basal metabolism was +1 per cent. Eleven months later patient remains well with a pulse of 72 per minute, no tremor, exophthalmos slight and feels fine. He shows marked gain in weight, up to 190 pounds from 118 before operation. His rate is −4 per cent and patient is working, taking thyroid extract, 2 grains, daily.

CASE XVII.—F. A., aged thirty-three years, female, married, showed the usual symptoms of thyrotoxicosis including exophthalmos. Her gland was moderately enlarged and showed bruits. Her basal rate was +47 per cent, pulse, 105 per minute and she was kept in bed ten days before operation under medical treatment.

A total thyroidectomy was done, convalescence was uneventful, and she left the hospital two weeks later with a pulse of 70 per minute, a basal rate of +2 per cent and feeling perfectly well.

Eleven months later patient feels fine, her pulse is 72, no nervousness, and she has gained weight. Basal rate, −1 per cent. No eye signs present. This patient became pregnant eight months after her operation. She takes 2 grains of thyroid extract daily.

CASE XVIII.—C. B., male, aged fifty-two years, married, showed nervousness, anginal attacks, tremor, loss of weight, shortness of breath, high blood pressure—200 systolic, 120 diastolic—and auricular fibrillation. His basal rate was 89 per cent but after medical treatment for two weeks with iodin his rate dropped to +12, but his fibrillation remained. At his own request he was operated on.

A total thyroidectomy was followed by a somewhat stormy convalescence

following partial starvation. This was relieved promptly by intravenous glucose and followed by a prompt convalescence.

On leaving the hospital two weeks later, he felt well, had gained weight, his pulse was regular and 72 per minute, basal rate normal with 4 grains of thyroid extract daily.

Eight months later the patient looked and felt well, his pulse was regular at 72 per minute, he complained of no shortness of breath or anginal pains, though his blood pressure had remained high.

CASE XIX.—C. J., aged twenty-one years, single, had thyrotoxicosis of the exophthalmic type showing a very large gland with loud bruits. Nervousness was marked with shortness of breath, tremor and stare. His pulse was 114 per minute; basal rate, +34 per cent and weight, 140 pounds.

On account of patient's cardiac condition, he received a month's preliminary medical treatment including iodin but did not show much improvement.

Total thyroidectomy was followed by a fairly stormy convalescence for a few days, but was then followed by rapid improvement.

This patient complained of feeling cold for some time during which period his basal rate was −29 per cent. This was brought up to normal with 4 grains daily of thyroid extract, his weight came up to 150 pounds and he felt well. However, his pulse remained fairly rapid 80 to 90 per minute and his vital capacity remained low, 66 per cent. The electrocardiagraph showed left ventricular preponderance.

Eleven months later patient was not nervous, his basal rate was −5 per cent. The symptoms he showed at that time were due to his cardiac condition. His vital capacity rose to 77 per cent, his pulse was still 80 per minute but he had gained in weight and was at work. He takes 1 grain of thyroid extract daily.

CASE XX.—W. J. L., male, aged thirty-five years, married, showed nervousness, palpitation, tremor and a moderately enlarged thyroid with bruits. Loss of weight was marked, his pulse ranged from 90 to 110 per minute, stare was present, basal rate was +45 per cent. This patient is of interest in that he had previously been pronounced cured by Roentgen ray. Under our care he had received a year of medical treatment including 30 Roentgen ray treatments with periods of improvement and remission until he was able to work.

Total thyroidectomy was followed by an uneventful convalescence. A month later his basal rate was normal with 1 grain of thyroid extract, pulse, 60 per minute and patient was at work feeling well.

After a further period of two weeks this patient's basal rate suddenly dropped to −28 per cent and he exhibited signs of hypothyroidism. His daily dose of thyroid extract was increased to 4 grains with prompt improvement. At present, eleven months after operation, the patient looks and feels fine and is working every day. He has a normal basal rate; pulse, 70 per minute and has gained weight. He is now taking 2 grains of thyroid extract daily.

CASE XXI.—A. L., aged forty-nine years, female, single, had been totally incapacitated for nearly two years. Progressive thyroid enlargement with exophthalmos and the usual nervous symptoms had occurred. The thyroid was large and showed bruits. Pulse, 102 per minute; basal rate, +69 per cent; weight, 122 pounds. Her vital capacity was 59 per cent and the heart showed left ventricular preponderance.

After preliminary medical treatment her rate dropped to +29 per cent and she showed marked improvement.

Total thyroidectomy was followed by an uneventful convalescence. She left the hospital less than two weeks later with a basal rate of −17 per cent and pulse of 76 per minute.

Two weeks later she had been taking 1 grain daily of thyroid extract—her rate was +8 per cent, she said she never felt better, and all her signs had disappeared. A letter received seven months after her operation states she is well and at work as before her trouble. She now takes 2 grains of thyroid extract daily.

Case XXII.—A. K., female, aged thirty-two years, married, showed markedly exaggerated symptoms of thyrotoxicosis including grave loss of weight, marked tremor and nervousness and a very large thryoid. Her basal rate was +70 per cent; pulse, 140 per minute; weight, 86 pounds. She made no response to iodin owing to previous prolonged course given her by her family physician. Rest was practically impossible to secure owing to extreme motor excitation.

At the end of ten days hospitalization she was operated on, developing postoperative thyrotoxic crisis with a pulse of 200 per minute, a temperature of 106° F. and respirations, 30 per minute. These symptoms were accompanied by markedly increased nervousness and delirium.

After seventy-two hours of intense therapy, intravenous glucose, saline, and so forth, she rapidly improved and on leaving the hospital six weeks later her pulse was 72 per minute, nervousness slight, no tremor, exophthalmos about 75 per cent diminished. Five months later patient showed no symptoms, had gained weight to 120 pounds and felt well. She takes 2 grains of thyroid extract daily.

In all of the cases, the operations were performed with the patient under light nitrous oxide and oxygen anesthesia and both sides of the neck were blocked by injecting 0.5 per cent novocain previous to making the incision.

While in many cases the proper balance is readily obtained by giving thyroid extract, in some cases considerably more time is necessary, even as long an interval as six months before the proper dosage and balance is arrived at. During the period of adjustment, however, these patients are in no way incapacitated.

In the cases of individuals with cardiac decompensation with enlarged hearts, with or without hypertension, definite cardiovascular sclerosis and lowered vital capacity—compensation was reëstablished in a remarkable manner, vital capacity increased and the patients got along surprisingly well with the basal rates reduced to below normal. To these individuals only small amounts of thyroid extract were given and no attempt was made to bring the rate up to normal or above, but remaining content with a rate slightly below normal.

Conclusions. 1. In selected cases of thyrotoxicosis at least, a total thyroidectomy is indicated, as we believe the entire gland is diseased. For all cases requiring operation a much larger amount of thyroid gland should be removed than has been customary. Since the date of our preliminary report[1] this is apparently becoming more widely recognized.

2. The postoperative reaction appears to be inversely proportionate to the amount of gland removed. This apparently applies likewise to the period of convalescence.

3. It is not difficult in cases of total thyroidectomy to maintain a proper thyroid balance with a thyroid preparation, if regulated from time to time by basal metabolic determinations. A number of these patients are able to determine subjectively the amount of thyroid extract they require. The length of time required to establish this balance varies with the individual.

4. In seemingly hopeless cases of exophthalmic goiter, the results of total thyroidectomy have been most gratifying. The patients after long periods of complete invalidism have resumed their usual occupations and enjoy good health.

5. The improvement in the decompensated cardiovascular patients following total thyroidectomy has been most gratifying.

6. We realize the number of cases upon which this report is based is not large. However, the uniformly good results appear to warrant this more complete report.

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STAMMERING PRODUCED BY THYROID MEDICATION.

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Tolerance to thyroid medication varies within a very wide range. The amount of thyroid that can be taken, without producing untoward effects, depends upon the autogenous thyroid content of the individual as well as upon his susceptibility and not upon his age or weight. At the present time we have no means of accurately measuring the autogenous content or the individual tolerance. While it is considered by some that the determination of the basal metabolic rate may be of value as a control in the administration of thyroid medication, Lawrence[1] at the recent meeting of the Association for the Study of Internal Secretions reported that in some of his cases symptoms of overdose developed before the basal metabolic rate reached normal. The clinical picture, therefore, supplies the best information as to the tolerance of any particular patient.

The reaction produced by the administration of thyroid beyond the point of tolerance is essentially that of an acute thyroiditis. The symptoms are generally manifestations of disturbances in the central nervous, gastrointestinal and cardiovascular systems and are expressed in the form of extreme restlessness, loss of sleep, crying spells, outbursts of temper, marked irritability, vertigo, headache, diarrhea, vomiting, syncope, tachycardia, flushed face, rapid rise in temperature and general exhaustion.

To this varied array of disturbances, the writer wishes to add that of temporary stammering. He has been unable to find any reference to stammering being produced by thyroid medication in any of the 340 cases reported in the American literature which he[2] recently reviewed nor in any which have been published since then.

The etiology of stammering is still a subject of controversy involving the question of whether the primary disorder is due to peripheral or central disturbance. Kenyon[3] feels that stammering is dependent on several factors such as nervous excitability, emotional susceptibility, tendency to muscular tension and formed habits. He states that in children the condition develops in those who appear to be physically and mentally normal in every way and that only rarely does it occur in the feeble minded. The opposite view is entertained by Nadoleczny[4] who claims that there are numerous physical and nervous degenerative manifestations which have been definitely established in stammerers. Hudson-Makuen,[5] in an analysis of 1050 cases, found that four-fifths of all stammerers are of average mentality and that only about one-fifth are below the average.

While it is outside the province of this report to enter into any controversial discussion, we are probably correct in stating that one of the exciting factors in the etiology of stammering may be nervous excitation. So that, even though we cannot rule out any other possible etiologic factors, it seems reasonable to assume that the stammering in our patients was a manifestation of an increased nervous irritability and part of a generalized nervous excitation produced by thyroid medication. This contention is strengthened by a consideration of the first case, that of Leonard, whom we were able to follow for a long time and thus study the situation at length. In this boy, the relationship between the stammering and the administration of thyroid extract was so marked that we could produce stammering at will, an increase in the dosage intensifying the disturbance and a decrease modifying or stopping it.

A few years ago William Browning[6] advanced the claim that stammering is primarily not a disorder of the central nervous system but that it is a phase of hyperthymism closely allied to status thymolymphaticus. According to him, there is generally a block in the thymic area attributable to thymic enlargement or thymic persistance. He was able to demonstrate in his cases of stammering an enlarged thymus both by percussion and by Roentgen ray

examination. Improvement followed roentgenographic treatment. He considers that this thymic enlargement contributes the immediate cause of the stammering and may be classed as an inhibitory reflex with the systemic and other influences acting as accessories. Roentgenographic studies of the thymus were made in each one of our cases but we were unable to demonstrate any hypertrophy at any time nor any difference in the size of the thymus between the active and quiescent stages of stammering.

Permanent stammering has its periods of activity and quiescence. The temporary character of the disorder in the children under observation, however, is emphasized by the subsidence and cessation of the stammering upon discontinuing treatment. After a quiescent stage of variable length, during which time no medication was given, the tolerance was later brought back through a gradual increase in the dosage. In the first case cited the previous tolerance was not reached until after a lapse of one year.

We are not in a position to state the reason for the sudden development of stammering in children who had been under treatment for a long period. It may perhaps be explained upon the basis of a cumulative effect.

The treatment of childhood myxedema and hypothyroidism in vogue at our endocrine clinic consists of starting with a small dose and then gradually increasing it every other week, at first twice a day, then three times daily. During the alternate weeks no medication is given. The first dose is $\frac{1}{10}$ gr. of thyroid extract, the next $\frac{1}{8}$ gr. $\frac{1}{4}$, $\frac{1}{2}$ and so on until 1 gr. of thyroid extract three times a day is reached. It is continued at this dose adhering to the alternation of one week. As the organotherapeutic products of the various firms vary in their methods of preparation and units of dosage, the product of the same firm is always specified so as to obtain uniform action. This method has proven very efficacious in the building up of tolerance and in the control of untoward symptoms.

Report of Cases. CASE I.—(Infantile myxedema). Leonard, aged ten years, first came under our observation at the age of seven years (September, 1924). The past history was one of delayed physical and mental development with eruption of the first tooth at thirteen months, sitting up at twelve months and walking and talking at three years of age. His growth appeared to be stationary from the third year on. His facies and general appearance was that of the classical picture of so-called sporadic cretinism, or as we prefer to term it, childhood myxedema.[2] He was short in stature and underweight, being 33 inches in height and 30 pounds in weight. The general musculature was poor in tone and turgor, the skin and hair dry, the teeth small and carious, the extremities cold and the abdomen distended and presenting an umbilical hernia. Pads of fat were palpable under the clavicles, around the ankles and in the cheeks. His mental age was below his physical age. He did not appear to be very much interested in his surroundings and showed a tendency to sleep a large part of the time, especially in the mornings.

He was placed on thyroid extract, $\frac{1}{10}$ gr. with a gradual increasing dosage as explained in the text. By January, 1925, he had improved to such an extent that he had gained 2 inches in height, had become more interested in his environments, played with children, did not sleep as much, shoveled snow and in general displayed signs of both physical and mental developmental progress. The pads of fat had disappeared. He was obtaining on that date 1 gr. of extract three times a day.

By February 6, 1925, six months after the onset of treatment, there was a marked improvement in his speech and vocabulary, but it was noted that he was beginning to stammer. No attention was paid to this condition and the thyroid was continued, being given on alternate weeks. As the subsequent history is important, it will be given in a little more detail.

February 18, 1925. Still stuttering. Increase of $\frac{1}{2}$ inch in height.

March 5, 1925. The general condition continued to improve with a growth of another $\frac{1}{2}$ inch in height. The mother noticed that the stammering was more marked while he was on thyroid. Thyroid extract was discontinued for two weeks.

April 5, 1925. The boy did not stammer when taken off thyroid but there was a general retrogression shown by a tendency to sleep, stationary weight and loss of his interest in his playmates. The thyroid was reduced to $\frac{1}{2}$ gr.

April 17, 1925. Stammering began again as soon as he was placed on thyroid and became so marked that his speech became inarticulate. His general nervousness increased. The medication was discontinued for the next three months. This was followed by a modification in the severity of the stammering, finally stopping entirely by July 10. He was placed on syrup ferri iodid for the iodin content for the summer and was next seen in September. He was sleepy, pale and not as bright as formerly but he was not stammering. Thyroid treatment was again instituted to be followed by a general improvement but accompanied by stammering. Medication was suspended again and by December, 1925, he had stopped stammering.

January, 1926. He was placed on $\frac{1}{10}$ gr. of thyroid and stammering was first noted on the twenty-eighth of that month but the treatment was continued because of the general condition which demanded thyroid medication. On March 18, 1926, the thyroid had to be suspended because of the severity of the stammering. He was then placed on pituitary substance, $\frac{1}{10}$ gr. twice a day with a gradual increase from then on. Under this second extract, there was an increase in height and weight but not as marked as that obtained with thyroid extract. The myxedematous appearance had returned. Thyroid medication was again tried, starting with $\frac{1}{20}$ gr. and with a gradual increase. He tolerated this much better so that he was able to take larger doses within a few months. His family physician took over the treatment from then on and reported that there was no return of the stammering within a few months.

Case II.—(Infantile myxedema). Joe, aged ten years, first came under our observation at the age of six years. He gave a history of a normal birth but at nine months of age the mother noticed that he was not developing as well as her preceding seven children. His physical and mental development from then on was retarded. His appearance when first seen at the clinic was also that of a typical myxedematous child.

Thyroid treatment was started October 9, 1924 and continued by our method until April, 1925, when stuttering and stammering were first noted. During this time he had improved to such an extent that his face appeared normal except when he laughed and then one could discern the myxedematous features. He spoke much better and his height had increased. His subsequent history is similar to the first boy's. Stammering continued as

long as he was on thyroid medication and subsided only when the extract was discontinued. This rise and fall in the stammering continued for eight months, becoming aggravated with an increase in thyroid and subsiding with a decrease. It was finally suspended entirely for several months and then resumed in small doses. The tolerance was regained and he is now on thyroid medication without any return of the stammering.

CASE III.—(Hypothyroidism). Milton, aged twenty-two months when first seen at the Clinic (March 19, 1925) gave a history of normal delivery, breast fed for seven months and then placed on formulas. The first tooth appeared at the age of ten months and when first examined he was unable to sit up by himself nor stand. He could not talk. He did not present a typical facies of childhood myxedema but his skin and hair were dry and abdomen was distended. Rachitic signs such as Harrison's groove, enlarged epiphyses and rosacea were found. A diagnosis of hypothyroidism and rickets was made and he was placed on thryoid extract, cod-liver oil and phosphorus and an appropriate diet for his age. Improvement was noted in two months. On June 14, 1925, he could sit up unaided and had begun to talk. On December 10, the general condition was improved but he began stuttering and stammering. He was obtaining 1 gr. of thryoid extract three times daily at that time and had been under treatment nine months. Thyroid was discontinued entirely but he continued to stammer a little until February 19. 1926 when it stopped. Treatment was resumed a month later and has been continued up to the present without any further recurrence of the stammering.

CASE IV.—(Infantile myxedema). Martin, aged ten years, was a typical case of infantile myxedema with a history of physical and mental development and delinquency. Thyroid treatment was instituted October 8, 1925, and continued until May 20, 1926, when stammering was first noted. The medication was discontinued at once and not resumed until three months later. The stammering had ceased in two months' time. On the resumption of treatment, thyroid extract was given in doses of $\frac{1}{10}$ gr. twice a day and increased very slowly on alternate weeks. The child has continued to improve during the past year without any recurrence of the stammering.

CASE V.—(Hypothyroidism). Bernard, aged eight years, gave a history of delayed physical development but did not appear backward until he was sent to school when it was noted that he did not do as well as the other children of his age. He was delinquent in his speech and his mentality. Treatment was instituted on March 19, 1926, and was followed by an improvement in his speech and in his school record. Stammering first appeared on December 16, 1926, after he had been on 1 gr. of thyroid extract for two weeks. This was discontinued and pituitary substance, $\frac{1}{10}$ gr. twice a day, was substituted. Stammering lasted for one month. Thyroid treatment was then resumed with small doses, with a later return to tolerance. His present condition shows a continued improvement with no return of the stammering.

Summary and Conclusions. The untoward symptoms produced by thyroid medication are essentially those of an acute thyroiditis and are generally disturbances of the central nervous, gastrointestinal and cardiovascular systems. Stammering may be produced by thyroid extract and should be considered as a manifestation of a general nervous excitation following disturbance of the central nervous system. When observed during the course of thyroid treat-

ment, it should be treated as any other toxic symptom by an immediate suspension of the medication. The administration of the thyroid should not be resumed until some time has elapsed after the disappearance of the stammering and then only with small doses.

Five cases of childhood myxedema and hypothyroidism are reported in which stammering occurred during the course of thyroid treatment. The relationship between the stammering and the medication is clearly apparent.

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SPINA BIFIDA OCCULTA AND MYELODYSPLASIA WITH UNILATERAL CLUBFOOT BEGINNING IN ADULT LIFE.

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Cases of unilateral or bilateral clubfoot coming on in later childhood or adult life are not very rare. The description of a case in which this deformity could be explained by a congenital abnormality of the spinal cord (myelodysplasia) may be worth recording, especially as the local therapy can in some cases be supported by a regional operation.

Case Report. A Chinese male, aged thirty years, gives a history of *pes equinovarus* developing during the last three years. Since the age of twelve years he has had a slight curvature and bulging of the lower part of his back. This, however, has not been progressive, but he complains of having had soreness of the back after prolonged work as a hawker.

Three years ago he sprained his left ankle, and although recovery seemed to take a normal course at first, he has never been able to walk quite normally, and gradually noticed that his left foot was drawn inward and that he had a tendency to walk on the outer side of the foot. He developed a wart (perhaps a callus mass) on the external aspect of the sole of the foot, which was treated by an old-fashioned Chinese doctor with drugs and needling (acupuncture), with resulting infection. This condition cleared up promptly under aseptic dressing in out hospital one year ago. An attempt was made also at that time to correct the clubfoot by means of a plaster cast, but blisters formed on the dorsum of the foot and the cast had to be removed.

In the past year the deformity of the foot has greatly increased and the patient has difficulty in walking more than a few yards because of the pain he experiences in the toes and foot when these structures have to bear the body's weight.

The patient admits that he had incontinence of urine up to the age of eighteen years. Except for this symptom, the kyphoscoliosis and the foot deformity, his history is negative. Venereal disease is denied. There is no history of alcoholism, no complaint of numbness or shooting pains and no urinary trouble at the present time.

Examination. On inspection we find that the left foot is held constantly in adduction and extension, and that the arch is very high. The toes are overextended in the metatarsophalangeal joints, and flexed in the phalangeal joints. The skin shows more pigmentation than that of the right foot, and shows several scars on the lateral surface, resulting from ulcers he had a year ago. When the patient tries to relax his foot, it is not possible to bring it into normal shape and position. The varus position can be nearly reduced, but it is not possible to reduce the extension, because of contracture of the tendon of Achilles; neither is it possible to reduce the high arch. The foot resembles that seen in Friedreich's ataxia, only in that disease there is no spasticity, and a slight pressure on the sole brings the foot back to its normal shape. The right foot is normal in shape, but its arch is rather high, and cannot be stretched out fully, so that on this side, too, a clubfoot is beginning to develop.

The Roentgen ray examination of the left foot shows a spectacular lesion, involving the entire fifth metatarsal, articular surface of the proximal phalanges of the fifth digit and cuboid, and probably also the proximal articular surfaces of the second, third and fourth metatarsals. The lesion of the fifth metatarsal consists of erosion and new-bone production. These changes must be considered as trophic.

The left leg is usually kept very rigid, and it was at first thought to be spastic; but after a few days of rest the patient often relaxes his muscles during examination. There is much wasting of the muscles of the left calf and anterior tibial group (circumference of left calf, 25 cm.; right side, 26.5 cm.) but no wasting of the thigh. When the patient is lying quietly in bed, fascicular contractions can be seen in the left calf muscles, in the left anterior tibial group, in the extensors of both legs, and in the left gluteal muscles. The muscles are not flabby, rather a little tense, especially the left calf, which probably shows some fibrosis, and a marked shortening of the tendon of Achilles.

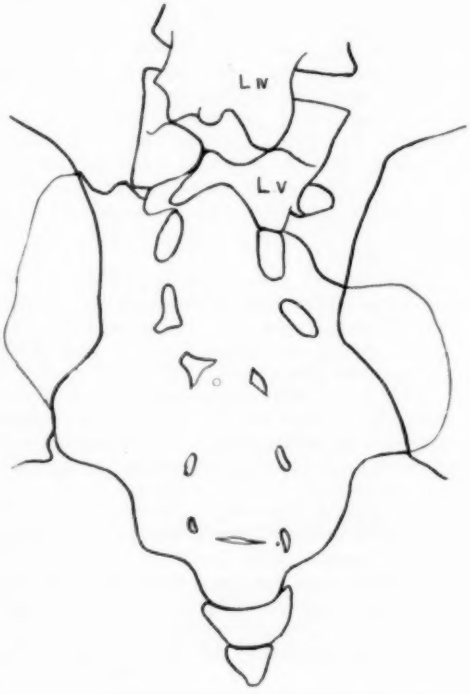
Voluntary movements in the ankle joint are reduced to adduction and very little flexion; abduction is not possible, neither is dorsal flexion. The power in the calf muscles is practically lost. Toe movements are still possible. The movements in the knee and hip joints are performed with normal power. The patient's gait is very peculiar: he tries to put as little weight on his left foot as possible, and keeps both legs very stiff. There is some degree of circumduction of the left leg, as in hemiplegia, but no tendency to hop on his right leg.

The patellar reflexes are present and equal in both legs; the Achilles reflex is absent on the left side, and low, sometimes absent on the right side. The plantar reflexes cannot be elicited.

Electrical examination shows a low irritability in nearly all the muscles of the left leg. This is most marked in the gastrocnemius, from which muscle only partial contractions can be obtained. Response to the faradic current is weaker in all muscles of the leg and thigh, except the femoral muscles. The left gluteal muscles also show weaker response to electrical stimulation than the muscles of the opposite side.

Sensation. Sensation to touch is normal on both sides, except a small area of hypesthesia over the external side of the left foot, and over the

left sole, where slight touch is not perceived as readily as on the other side. Sensation to pain is diminished over the same area, but there is no total analgesia. Temperature sensation shows greater disturbance: on the left side the back of the foot, the external side and the sole are anesthetic to heat and cold, and this area of thermanesthesia goes up on the posterior part of the leg to a level half way up the thigh, thus having its distribution mainly in the first and second sacral segments. On the right foot, we find a small area of hypothermanesthesia on the external side. Deep sensibility is normal.



EXPLANATION OF FIGURE.

The dorsal lamina of the fourth lumbar vertebra is seen to be normal; the dorsal lamina of the fifth is small, and probably cleft. The sacral bone is not closed in the posterior median line. The intervertebral disks of the lower sacral vertebræ are still present. (From Roentgen ray film.)

Inspection of the Back. There is a marked scoliosis of the spinal column to the right, with the top of the curvature at the left of the twelfth thoracic vertebra. On palpation, the spinal process of the fourth lumbar can be felt, but below that point the finger falls into a groove, lying in the median line and extending downward over the sacral region. Firm pressure in the region of the first sacral vertebra is distinctly painful, and gives the palpating finger the impression of a cleft in the dorsal arch of the sacrum (spina bifida occulta). The Roentgen ray gives interesting additional data (see figure). The scoliosis is very marked, but no erosion of the bodies of the vertebræ in this region is made out. The photograph gives the impression that the scoliosis is due to a deformity at the right side of the lumbosacral joint, without any particular lesion of the sacroiliac joint. The

dorsal laminæ of the sacrum are open, and there is atrophy of bone at some places, with congenital abnormality of the fifth lumbar and upper sacral segments. Incomplete sacral fusion is well visualized on the Roentgen ray plate. The trophic changes in the bone with compensatory scoliosis probably developed during childhood. The scoliosis remains when the patient is lying on his back, but can be partly reduced by pressure.

Neurologic examination of the other parts of the body is essentially negative. Vision is good; the eye-ground shows nothing abnormal. The pupils are round, equal, and their reactions are prompt. The eyeball muscles function normally. No changes are noted in the other cranial nerves; hearing is good; no atrophy or fibrillary contractions in the tongue.

The arms are not atrophic; voluntary movements and power are normal; the reflexes can be obtained easily. Sensation is normal in all its qualities, there is no trace of syringomyelic dissociation of sensation. The abdominal reflexes are present in all levels; electrical stimulation of the abdominal muscles gives equally strong contractions on both sides. No urinary trouble exists at present; the sexual power is normal. Except for the skin and bone changes, no trophic or vasomotor disturbances can be found.

The patient's mentality is perhaps childish, and his intelligence is probably below the average, but he is alert. The strange spasms in his legs are probably of psychic origin.

The laboratory findings are essentially negative: Wassermann in the blood negative; the urine is free of albumin, sugar and casts; the white blood count is 8200; hemoglobin, 70 per cent. Lumbar puncture was not done, because there was no special indication, and we were uncertain as to the tissues that fill up the lower part of the vertebral canal, fearing such factors as an abnormally long spinal cord and spongeous venous plexus.

Exploratory laminectomy was advised with the expectation that conditions could be corrected so as to check the progression of the symptoms, and especially to prevent the development of similar symptoms in the right leg. At operation, the arch of the fourth lumbar vertebra was found to be very small, with an opening on one side. The arches of the fifth lumbar and first sacral vertebræ were also found to be abnormal. Under the arch there lay a yellowish, tough tissue, about 2 cm. broad, covering the dura and pressing it. A second mass of the same structure was found beneath the arch of the fifth lumbar vertebra. The dura was then fully exposed from the first sacral to the third lumbar segments, four arches being removed entirely. The dura was apparently normal, but no pulsations could be seen.

Three weeks after the laminectomy, the Achilles tendon was lengthened and tendon transplantations done, to get the foot in good position and condition for movement. Six weeks after this second operation the foot has still a very high arch, but no equinus position. Slight movements are possible. The legs are not stiff.

Summary of the Case. 1. Cleft in sacrum and probably congenital anomaly of fifth lumbar vertebra, with trophic bone changes.

2. Occasional enuresis from childhood until eighteen years of age.

3. Kyphoscoliosis, noted for the first time at the age of twelve years.

4. After slight trauma, progressive clubfoot on left side, developing during the last three years, with trophic changes in the bones.

5. Wasting of the muscles of left leg, with fascicular contractions, low electrical irritability and contracture of gastrocnemius.

6. Achilles reflex absence on left, and very low on right side.

7. Loss of temperature sense and slight disturbance of pain sensation, left and right.

8. Beginning spasm in the right foot.

Discussion. In discussing this case, it is not my object to give detailed references to the literature, but as cases of this kind are seldom reported in American literature, a brief summary may be of use.

The name spina bifida (or spina bifida aperta, cystica) has been given to cases of cleft of the arches of vertebræ with bulging of the skin in which tumor, meningocele or myelocele might be found. We use the name spina bifida occulta (Virchow) for those cases in which no tumor existed, and where inspection does not reveal the true condition of the bone. Virchow pointed out that this condition is often accompanied by hypertrichosis in the lumbosacral region and that also changes of the spinal cord are very common.

Spina bifida, therefore, is more than the simple cleft in the arches of some vertebræ. It means that there are also changes in the mesoblastic and nervous tissues.

The name myelodysplasia has been given by Fuchs to those cases of congenital defect of the lumbosacral part of the spinal cord which form in themselves a clinical group, characterized by one or more of the following symptoms: (1) Weakness of sphincters, mostly as enuresis persisting into adult life; (2) syndactilism of the second and third toes; (3) disturbances of sensation in the legs of dissociated type, of which thermanesthesia is most marked; (4) cleft of arches of one or more vertebræ; (5) abnormal skin and tendon reflexes of abdomen and lower extremities; (6) deformities of the feet, clubfoot or flatfoot, often with trophic and vasomotor disturbances. Later Fuchs added: (7) Skin changes, such as hypertrichosis, nevus and fovea coccygea. Fuchs does not discuss the question of changes beginning during childhood or adult life, but speaks mainly of congenital abnormalities.

This makes it evident that myelodysplasia is only that group of the spina bifida cases in which the chief feature consists not in changes merely in the vertebral column, but in a considerably larger group of structures. According to some authors, spina bifida with tumor occurs in one of every 1000 births; cleft of more than the fourth and fifth sacral vertebræ, however, is found in 18 per cent of sacra (series of Radlauer, see Holmdahl).

These statements deal only with congenital cases. It has been known for a long time, however, that in a number of cases symptoms began to develop during childhood or even adult life. Froriep and Förster report the case of a woman aged nineteen years, in whom at the age of six years a small sacral tumor began to grow and at the same time bilateral clubfoot developed. Many similar cases have been reported also with tumor formation in the lumbosacral region, and several of these authors discuss the probable changes in the spinal cord. These changes can be divided into two different groups:

Those due to some mechanical factor, such as pressure on the cord or cauda roots, caused by membranes or lipomatous growths (often a myofibrolipoma has been found), and those due to some structural abnormality in the cord itself. The examination of the lumbosacral cord in cases of spina bifida occulta (Utchida) or myelodysplasia (von Frankl-Hochwart, Chiari) may reveal an open central canal with hydromyelia, or a double central canal, accompanied by a varying degree of fibrous glia proliferation, which may at times extend even into the gray matter. In extreme cases, when this glia proliferation is the main feature, we may use the name lumbosacral syringomyelia; but it will be evident that there are many transition forms with a slight neuroglia-fiber production around the central canal, in already existing congenitally deformed nervous tissue, which do not fall under that diagnosis. I would suggest using the term myelodysplasia also for these cases in which progressive symptoms exist, but are largely of trophic nature and do not give the typical progressive atrophies and sensory disturbances of syringomyelia.

The combination of congenital clubfoot and spina bifida has often been described. Clubfoot, however, coming on during later childhood or adult life is not so often seen. Bibergeil mentions the combination as occurring rather often in those cases of clubfoot which begin after the age of seven years. The development of the foot deformity seems to begin often after a trophic ulceration (mal perforant) which in many cases (Brickner, Beck and Katzenstein) is the first sign of myelodysplasia. Beck also gives the report of a case in which the clubfoot was unilateral and began to develop after an injury of the foot. In Jones' case no cause could be found for the development of the clubfoot.

Paresis and atrophies of muscles of the legs are also noted as a symptom in this disease. They begin in some cases in adult life (Hoelen, Hottinger, our case) or are present from early childhood (Hassin, Clark).

Spastic symptoms in the legs were seen by a number of authors. In Robertson's case these symptoms began after an injury to the back, and the patient developed signs of typical pyramidal tract lesion, with clonus and Babinski's sign. The cleft was located in the first sacral vertebra, but a large nevus covered the back at the level of the second to fourth lumbar vertebra. Beck, Hassin and others described similar syndromes.

The most common symptom is incontinence of urine (Mattauschek, Chiari, Spiller, Lichtenberg, Katzenstein, Brickner). This trouble in some cases dates back to childhood and gets worse afterward, or it may appear at a later age. Several of these cases have been operated upon with good results.

Operation on the spine was done as early as 1890 by Maas, and in 1891 by Jones, in the latter's case for progressive clubfoot, with a very good result. The operation has been done in most cases for

enuresis (Katzenstein) or trophic ulcers; in Hoelen's case for progressive atrophies. When fibrous bands have been found pressing the roots or the lower part of the cord (which may reach downward to nearly the fourth lumbar vertebra), or when the roots have been found to be stretched out and fixed at their points of emergence through the membranes, the result has often been very good; but when nothing but a fatty mass has been found surrounding the cauda equina the operation has usually been futile. These last cases probably were those where organic changes of the spinal cord were the cause of the symptoms.

Since we have no means up to the present time of deciding which form of anatomical abnormality is present in a given case, it seems advisable, according to Brickner, to consider operation in every progressive case.

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NEGATIVE PRESSURE IN EPIDURAL SPACE.*

Preliminary Studies.

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and

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With ordinary equipment, on withdrawal of the stylet of the lumbar puncture needle, some spinal fluid escapes before the manometer can be attached. Barring accidents, this loss is small, never

* Presented as an exhibit before the Clinical Congress of the Seventeenth Annual Session of the American College of Surgeons, Detroit, October 3 to 7, 1927.

more than a few drops. Nevertheless, some observers are of the mind that the loss of even a few drops of fluid might represent an appreciable reduction in spinal-fluid pressure. As a result, their efforts have been bent toward constructing manometric devices designed to estimate spinal-fluid pressure immediately upon withdrawal of the stylet. However, it occurred to us that these special attachments were unnecessary, and we believed that a needle, without stylet, and with manometer directly attached could be pierced even through all the tissue interposed between the skin and the spinal canal without plugging the needle. Certainly no difficulty should be experienced if the stylet were not removed until reaching the ligament between the vertebral laminæ.

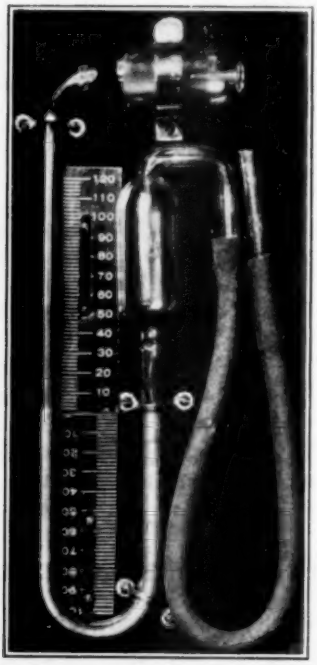

FIG. 1.—Trial manometer devised to record negative as well as positive pressures.

In accordance with that belief, a mercury manometer was attached directly to a spinal-puncture needle, and with this arrangement of apparatus a spinal puncture was attempted. We were successful. However, just before the puncture was completed, which, of course, would be indicated by a positive pressure, we noted a sudden declination of the mercury in the manometer. Several punctures were executed with the same technique prevailing, and in every instance our original observation was confirmed. This manometric declina-

tion was construed as evidence of a negative pressure existing in the cavum epidurale. This proved to be the correct localization, since in our experiment upon a cadaver, india ink injected through the spinal needle after a negative pressure had been encountered, was demonstrated in this cavity by dissection.

Feeling that this negative pressure might be considerable, we had a U-type mercury manometer constructed which would record negative as well as positive readings. The results of fifty observations are given in Fig. 2. Fig. 1 shows the manometer devised by us for this study.[1]

In the diaphragmatic sinus, a negative pressure obtains, probably on the basis of a postfetal separation of the visceral from the parietal pleura, induced by the progressive assumption of more obliquity on the part of the costal planes and by the growth of the thoracic box

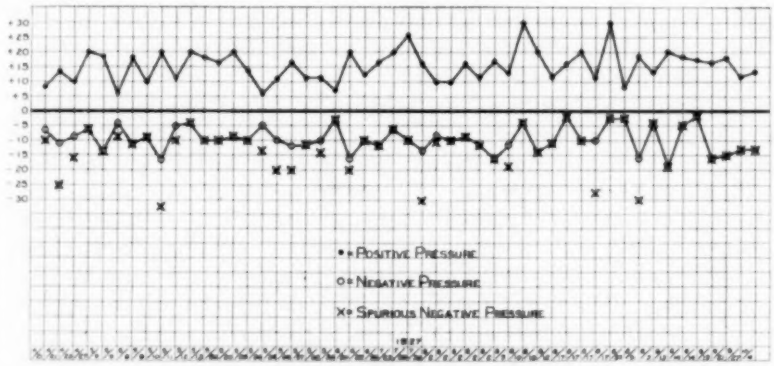

Fig. 2.—Negative pressure in epidural space. Curve of observations, 50.

out of proportion to its contents. We are of the mind that this negative pressure is perpetuated, not by the elastic retraction of the lung, nor by the rarefying influence of inspiration (since it is also present to a lesser degree in quiet expiration), but, first, by the fact that most of the oxygen circulating with the blood is combined as oxyhemoglobin, which is not proportionately dissociable with small reductions in oxygen tension, and therefore not available in its entirety for diffusion, and second, by the presence of a diminished gaseous tension in the tissues surrounding the diaphragmatic sinus, resultant from their energetic cellular metabolism. Thus far, we feel that a similar mechanism may explain the genesis of the negative pressure in the cavum epidurale, the existence of which has its modus operandi in the late embryonic and postfetal extension of the spinal column incorporating in the development, because of its

[1] The manometer was constructed for us by Becton, Dickinson & Co., Rutherford, N. J.

more rapid growth, a caudad elongation of the vertebral canal away from the conus terminale of the slower-growing and cephalad-fixed cord.

Spinal Fluid Seepage. Discovery of negative pressure in the cavum epidurale whetted our curiosity in regard to the probability of spinal fluid seepage from the perforation made in the dura by the lumbar puncture needle. The following also stimulated us. One of us (Heldt) has observed in carrying out several lumbar punctures on two different patients, an exudate of spinal fluid on the surface of the skin after the withdrawal of the needle. Even after the drop was wiped away another would gradually ooze out. The other of us (Moloney) has noted on two different occasions a fairly free flow of spinal fluid from the large barrel of the Hoyt needle which had been perfectly dry previous to the perforation of the dura by the smaller cannula. Finally, Scarlett, one of our hospital staff associates, reported to us that he had heard distinctly a hissing ingress of air concomitant with the tapping of the epidural space surrounding a shriveled multiple-sclerotic cord.

To study this problem, we selected a spinal puncture needle equipped with a stopcock. When such needle is inserted to the depth of the ligamentum flavum, the stylet is withdrawn and the spinal manometer attached. To the stopcock of the needle, we attached, by means of rubber tubing, an ordinary 5- or 10-cc. Luer syringe loaded with normal saline solution. The needle is then thrust forward slowly until a negative pressure is recorded by the manometer. The tap of the stopcock is now turned until communication is established between the barrel of the needle and the syringe. Then it may be noted that normal saline is aspirated into the epidural space until the negative pressure disappears. Should the negative pressure be small, −6 mm. of Hg. or less, aspiration does not occur but a little pressure on the plunger of the syringe causes ingress of the saline and consequent equalization of pressure to zero or slightly above. Thus far in our studies, only small amounts of saline have been injected, 6 cc. being the largest quantity; with the perfection of our technique, however, we judge that much larger quantities may be instilled.

With not only a definite epidural space about the dural confines of the spinal fluid but also a negative pressure, we believe it highly probable that spinal fluid seepage may be a factor in the production of lumbar puncture headache. The elusive etiology of lumbar puncture headache is engaging considerable of our present time, thought, and effort. Studies incorporating the foregoing facts and implications of negative epidural pressure and of spinal-fluid seepage are in progress. Other angles of attack are suggesting themselves as the studies proceed. We hope to learn something about the causal factors of this discommoding and fear-inciting headache.

Spurious Negative Pressure. We erred in our first conception relative to the magnitude of the negative epidural pressure. Subsequent observations have taught us that the negative pressure that we found was not due entirely to the causal factors previously outlined, but that its major component was, in most cases at least, an artefact, explainable by the pinching of the intradural cavity and its contents between the anterior wall of the spinal canal on the one side and the invading lumbar puncture needle prior to its perforation of the dura on the other side. Quite obviously this compression of the intradural cavity and contents would increase the epidural space at the site of the needle, would so reduce its pressure, and would be no more than an index of the resiliency and toughness of the dura or the sharpness of the impinging needle.

We encountered no difficulty in establishing the presence of this spurious negative pressure, nor in differentiating it from the true negative epidural pressure. With just the tip of the needle in the cavum epidurale, there is an unvarying negativity ranging from −1 to −18 mm. of mercury (in our present series). This is the true negative pressure. However, when the needle is projected against the dura, the artificial factors for rarefaction mentioned above are brought into play. These are disclosed by a sudden decline in the pressure. This declination is directly proportional to the amount of the impingement, and is the arithmetical sum of the true and the spurious negative pressures, and often exceeds a negative 30 mm. of mercury before the dura is pierced. This fact is readily made manifest by moving the spinal puncture needle back and forth and watching a proportionate rise and fall of the mercury in the manometer. We have never found the true negative epidural pressure to be numerically more than the true spinal fluid pressure.

So far, most of these studies have been solely of academic interest. There is, however, a decided advantage in doing lumbar punctures with a needle bereft of stylet as the target is approached and with the manometer directly attached. In obese subjects, or subjects with scoliotic, lordotic, or kyphotic spines, encountering the negative pressure indicates that the tip of the needle is in the cavum epidurale, and that one slight thrust forward will suffice to puncture the dura. We do all our routine spinal punctures after this fashion, and we have found it to be a simple time- and disposition-saving method, to say nothing of its worth in maintaining the integrity of many patients' backs, which otherwise, as the experience of many other lumbar puncture operators will confirm, we are sure, might be comparable to sieves from too ardent endeavors to obtain spinal fluid.

Summary. 1. Evidence is offered to show that there is normally a negative pressure in the epidural space.

2. Spinal fluid seepage into the epidural space through perforation of the dura by lumbar puncture needle on account of this negative pressure is probably a potent factor in the causation of lumbar puncture headache.

3. Lumbar puncture may be simplified by withdrawing the stylet from the needle on reaching the ligamentum flavum, attaching the manometer at that point, and using the negative pressure of the epidural space for local orientation.

TREATMENT OF DIABETES WITH AN ACID–ALCOHOLIC EXTRACT OF PLANTS RICH IN VITAMIN B.

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That vitamin B possesses the power of stimulating the utilization of glucose in the body is an idea which gradually has taken shape in my mind, as a result of an observation of its action in almost four years of clinical use. Beginning its use for the purpose of stimulating the appetite and rate of growth of children, I found it not only very effective in that connection, but also in adults, often securing a gain in weight of as much as 2 to 2½ pounds a week in undernourished conditions, with a corresponding increase in appetite. Along with this stimulation in children and adults, there was evident a marked diminution in the occurrence of upper respiratory infections. Since this increased food utilization, growth and resistance to infection is attained in diabetes through the use of insulin it seemed logical to assume that the vitamin might be exerting a similar action.

In the winter and spring of 1925–1926 vitamin B was tried as an adjunct to the dietary treatment of diabetic patients in the Outpatient Department of the Cincinnati General Hospital, and results were obtained which indicated a definite effect. In some cases the vitamin seemed able to replace insulin up to about 15 units daily. However, the work was not sufficiently well controlled to report, and it is only this spring that definite data have been obtained on hospitalized patients under complete dietary control. Seven diabetic cases treated in this fashion are here reported, and it is hoped that a further series may be reported later.

That vitamin B is necessary for glucose utilization is not a new idea. In 1913 Funk[1] found that the symptoms of vitamin deficiency in pigeons were in direct relation to the amount of carbohydrate eaten. Braddon and Cooper verified this in 1914.[2] In 1914 Funk

and von Schönborn[3] also discovered a hyperglycemia and diminution or absence of liver glycogen in polyneuritic pigeons, and that the administration of an yeast extract corrected these abnormalities. The presence of this hyperglycemia has been verified by Hirai[4] and Redenbaugh,[5] while Winter and Smith[6] and Funk and Corbitt[7] have further described the blood-sugar-lowering effect of yeast extracts on normal rabbits as well as polyneuritic pigeons. As further evidence that vitamin B deficiency interferes with glucose utilization, several investigators[8, 11] have reported a marked lessening of the heat production and respiratory quotient in such deficiency conditions. McCarrison[12] believes that pancreatic insufficiency is an important factor in producing the symptoms in vitamin deficiency. He describes an atrophy of the pancreas, with gastrointestinal disturbances referable to a loss of the external secretion of this organ. The islands of Langerhans he found normal in appearance. He makes no mention of diabetes mellitus as being on such a deficiency basis.

Kon and Drummond[13] have recently shown that when pigeons are allowed to eat only as much as they desire of a diet deficient in vitamin B, they do not develop any more of a hyperglycemia than do other pigeons fed on similar amounts of food containing this vitamin. They therefore conclude that hyperglycemia is not a part of the picture of vitamin B deficiency. Other authors[1, 2, 3, 4] have pointed out that there is a relationship between the vitamin B requirement and the food intake, the hyperglycemia developing on forced feeding with food deficient in this vitamin. From these facts it would appear that the loss of appetite may be due to an inability of the body to handle the vitamin-deficient food. This would give a purely metabolic basis for the explanation of the effect of vitamin B in so markedly increasing the appetite in animals and men.

Collip,[14] at about the same time as Winter and Smith and Funk and Corbitt, described the production of marked hypoglycemia in animals by the injection of an yeast extract. He went further, however, and found that a variety of plants (onion, lettuce, green beans, wheat leaves, and so forth) yielded a similarly potent extract. These extracts he found also effective in lowering the blood sugar and sugar excretion in depancreatized dogs. In no case did he mention giving the extract by any way except subcutaneous injection. His conclusion is that the active material is similar to insulin in its basic action. He does not consider vitamin B as a factor in the action of his extracts, but suggests the term "glucokinin," referring only to the carbohydrate metabolizing action. So far he had not reported its use in the treatment of human diabetes.

In our preliminary work, we have made use of an extract prepared from a mixture of plants, including some of those used by Collip. Our extract has been given both orally and subcutaneously, but has never produced a hypoglycemia; nor has it any effect on the sugar metabolism in depancreatized dogs. It is shown, however, to

affect markedly sugar utilization in normal and diabetic conditions when the pancreas is present and when the extract is given orally.

The preparation used was made by acid-alcoholic extraction of a number of plants known to be rich in vitamin B (alfalfa, sweet clover, corn silk, onions, carrots, spinach, rice polishings and bran). Approximately 40 per cent ethyl alcohol containing 0.4 per cent HCl was used in the extraction. The application of heat was avoided throughout the process. After the extraction was completed NaOH was added to bring the reaction almost to the neutral point, and the protein precipitate thus formed filtered off. For diabetics this alcoholic extract was used, but for children the alcohol was evaporated at room temperature and glycerine (to 40 per cent) added as a preservative. In the work reported in this and the following paper, the method of Folin and Wu[15] was used throughout for estimating blood-sugar values, and Benedict's[16] quantitative solution for urinary sugar.

Case Reports. Case I.—C. H. C., (14721) a Chinese male, aged forty-three years, was admitted to the Peking Union Medical College Hospital September 1, 1926, with a history of polydipsia, polyphagia and polyuria for one and a half years, and a chronic productive cough with rapid weight loss for the last five months. Physical examination showed extreme emaciation, some edema of the legs, and extensive pulmonary tuberculosis, active in both upper lobes, with cavitation on the left. Tubercle bacilli were present in the sputum. A low-grade fever with afternoon exacerbations was present. The urine contained 6 per cent sugar but no acetone. Fasting blood sugar was 133 mg. per cent, with a typical diabetic glucose tolerance curve.

On a diet of 1520 calories (fatty acid-glucose ratio of 1.2) for nine days, with insulin gradually increased to 24 units daily, the sugar output declined from 125 gm. to about 5 gm. and the fever abated somewhat. The body weight, however, fell from 40.1 to 37 kg. The diet was increased to 1780 calories (same ratio) and the insulin to 30 units daily. The urine became sugar-free and the temperature almost normal, although there was no gain in weight. The diet was gradually increased to 3000 calories, the ratio being shifted to 2.5, so that the increase was all fat, there being an actual reduction in carbohydrate. Protein was kept at 60 gm. daily. On this diet the patient kept sugar-free as long as 30 units of insulin were given daily, and the body weight rose from 37 to 48.5 kg. Roentgen-ray examination of the lungs showed marked fibrosis and healing of the lesions, and in every way the patient was much improved.

About December 1, an exacerbation of the fever interfered with his appetite and the food intake was irregular, averaging about 1750 calories, with 70 gm. protein and 35 gm. carbohydrate. The insulin had to be increased to 40 units daily to keep the urine sugar-free. The body weight was maintained. Early in January the patient decided he would leave the hospital before the Chinese New Year (February 2) and, since he could not safely administer the insulin at home, we decided to try vitamin. He was given 15 cc. each morning before breakfast for one week along with 40 units of insulin. The insulin was then discontinued and the vitamin dosage doubled for his remaining eight days in the hospital. On discharge his urine was still sugar-free. Previous reduction of the insulin to 30 units (without vitamin) had resulted in prompt glycosuria.

At his home he continued to take the vitamin and remained well for about two weeks, but the supply became exhausted and within three weeks his fever returned, hemoptysis occurred, and he was readmitted to the hospital February 22, 1927. His body weight had declined 1.5 kg. since leaving the hospital. With rest in bed and a diet of carbohydrate, 90 gm.; protein, 60 gm.; fat, 200 gm.; his sugar output varied from 70 to 115 gm. daily. His further course with, and without, vitamin is shown in Chart I. It is seen that his sugar excretion rapidly fell from 115 gm. to approximately 12 gm. a day, and was maintained at this low level so long as the vitamin administration was continued. When the vitamin was stopped it promptly rose and remained between 50 and 70 gm. He was now given a portion of the same vitamin solution which had been alkalinized with NaOH, heated

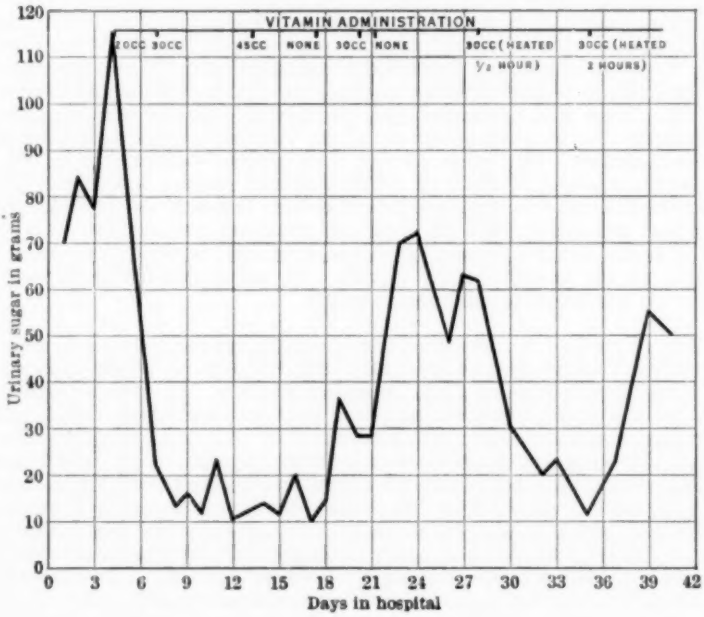

CHART I

to 80° C. for thirty minutes and then reacidified with HCl. Such treatment of the extract is seen to have been without effect on the vitamin activity. However, a second portion alkalinized, heated to 85° C. for two hours in a water bath, and reacidified, lost its effectiveness. Such treatment is known to destroy the activity of vitamin B. At this point the supply of active vitamin became exhausted.

CASE II.—C. H. M. (15769), a Chinese male, aged sixty-two years, was admitted to the hospital for the treatment of chronic glaucoma. He had no symptoms of diabetes beyond a mild polyuria which had been present for twenty years. His urine on admission contained 8 per cent glucose and the fasting blood sugar was 250 mg. per cent. His weight was about normal for his height. On a diet of carbohydrate, 50 gm.; protein, 50 gm.; fat 150 gm. (1750 calories); his sugar output gradually dropped from over 100 gm. daily to about 6 gm. and the blood sugar to 133 mg. per cent. When the

output became somewhat constant for several days between 5 and 8 gm. he was given 5 units of insulin daily, the diet remaining unchanged. On the third day of insulin treatment the urine was sugar-free. The insulin was stopped after the fourth day, and he at once began excreting 4 gm. of sugar daily. Three days later he was given 30 cc. of the vitamin solution and on the first day of it, and thereafter, the urine contained no glucose. He was discharged February 22, with instructions to continue taking the vitamin daily, but no word has been received of him since he left Peking.

CASE III.—W. T. M., (16254) a Chinese male, aged forty-nine years, was admitted to the hospital March 5, 1927, with a history of fever, productive cough and loss of weight for ten months, and polyuria, polyphagia and polydipsia for the last four months. Physical examination revealed far advanced pulmonary tuberculosis. His weight was 51.8 kg. and his height 67 inches. Kept on a diet of carbohydrate, 85 gm.; protein, 60 gm.; fat, 205 gm. (2425 calories) for six days his sugar output dropped from 60 gm. daily to about 15 gm. and the fasting blood sugar from 250 mg. per cent to 117 mg. He ran an irregular low-grade fever and the body weight declined 1.8 kg. After this preliminary six-day period, his diet was continued unchanged, but he received 10 cc. of the vitamin solution each morning before breakfast. On the second day of its administration the fever began to mount, reaching 39.4° C. on the fifth day of vitamin treatment. The sugar output also rose for two days, but then began to decline while the fever was still rising. On the sixth day the fever was evidently abating and it looked as though we might expect material improvement, but the patient left the hospital against advice. He had gained 1.5 kg. in weight under the vitamin treatment before he left.

CASE IV.*—L. T. Y., (14607) a Chinese male, aged fifty-six years, was in the hospital for study and treatment from August 24 to September 18, 1926, and from November 29 to December 20, 1926. He gave a history of polydipsia and polyuria for twenty-five years, but had never had a urine examination until two and a half months before admission, when sugar was found. Physical examination was essentially negative so far as it relates to this report. His height was 71 inches and his weight 90 kg. During his first stay in the hospital his urine could not be made sugar-free even on a basal diet and 7 units of insulin daily, although his body weight declined 5 kg. The sugar output declined from 80 gm. daily to about 6 gm. but to a lower level than this it was brought with great difficulty. On his second admission this was found to be due to an associated renal diabetes, since it was proven that excretion of sugar occurred at various times with a definitely subnormal blood-sugar level (66 mg. per cent). So far as we could estimate, 6 to 8 gm. of urinary sugar could be accounted for on the basis of the low kidney threshold. On his second discharge he was placed on a diet of carbohydrate, 65 gm.; protein, 110 gm.; fat, 265 gm. (3085 calories) which has since been adhered to quite strictly. The treatment and results are summarized in Table I.

From the data presented in this table it is seen that the patient's tolerance is approximately represented by the 2140 calorie diet. With increases beyond this the urinary sugar rises. When placed on the 3085 caloric diet, 45 units of insulin were required daily to avoid excess of urinary sugar for the first week, then 35 units were found sufficient, and finally 30 units. Stopping the insulin entirely and giving 15 cc. of vitamin solution, we see

* After this patient's discharge from the Peking Union Medical College Hospital he was under the care of Dr. J. A. Curran at Tunghsien, China, where the studies were continued along the same lines as in the Peking Union Medical College Hospital.

the sugar remaining about the same, while the next day 30 units of insulin alone caused the lowest figure obtained with this diet. The next day 18 units of insulin and 15 cc. of vitamin also gave very low excretion. Thereafter for the next six weeks, on 15 to 30 cc. of vitamin and no insulin, the excretion averaged only 10 gm. daily. When the vitamin was stopped on March 10 the urinary sugar rose steadily until March 22, reaching 16 gm. on that day. This rise seemed to be due to a spell of rainy weather which kept the patient indoors, since the next week was fair and the sugar again declined to around 10 gm. April 22 to 25 he was again given a hospital diet (of the same composition as he had been taking) and his sugar output was found to be around 14 gm. daily. He had regained all the weight lost during his stay in the hospital, and was feeling very well.

TABLE I.—CASE IV.

Date.	Diet.				Body wgt., kg.	Insulin, units.	Vitamin, cc.	Blood sugar, mg., per cent.	Urine sugar, gm., per day.
	C.	P.	F.	Cal.					
Aug. 24 to Sept. 1, 1926	70	50	170	2010	90	0	0	200	80 to 16
					89	0	0	133	
Sept. 2 to 13	60	40	160	1880	86	0	0	71	6 to 8
Nov. 29 to Dec. 4	45	50	185	2045	88	0	0	133	7 to 10
Dec. 5 to 17	35	50	200	2140	86	0	0	66	5 to 7
						15	0	111	4 to 5
Dec. 18	45	60	207	2280	..	0	0	....	9
Dec. 19	50	65	240	2620	..	0	0	....	14
Dec. 26, 1926 to Jan. 6, 1927	65	110	265	3085	..	45	0	....	7
Jan. 7 to 24	65	110	265	3085	..	30 to 35	0	....	7
Jan. 25	65	110	265	3085	..	....	15	....	7 8
Jan. 26	65	110	265	3085	..	30	....	....	5
Jan. 27	65	110	265	3085	..	18	15	....	6
Jan. 28 to March 10	65	110	265	3085	..	0	15 to 30	111	10
March 10 to April 1	65	110	265	3085	..	0	0	....	12
April 22 to 25	65	110	265	3085	95*	0	0	133	14

CASE V.—P. J. (3984), a Chinese male, aged thirty years, was admitted for study August 2, 1927. He had had glycosuria on two previous admissions in January, 1922, and June, 1927, and at the latter time he was suffering from a gluteal abscess. Fasting blood sugar in June was 133 mg. per cent. On August 2, the blood sugar was 125 mg. He was placed on a diet of carbohydrate, 110 gm.; protein, 70 gm.; fat, 200 gm. for the succeeding three weeks. The sugar excretion varied from 3 to 10 gm., daily for five days, after which he was given 4 cc. of the vitamin extract daily. The glycosuria diminished steadily, the urine becoming sugar-free on the fifth day and remaining so as long as this diet was continued. On the second day that the urine was sugar-free, the fasting blood sugar was 111 mg.

CASE VI.—H. M. K. (17405), a Chinese male, aged fifty-eight years, was admitted to the hospital July 12, 1927, with a history of tingling and itching of the skin for about one year, and with a constant glycosuria. He was kept on a full diet for three days, the sugar excretion varying between 43 and 78 gm. daily, and the fasting blood sugar being 222 mg. On July 15 he was placed on a diet composed of carbohydrate, 160 gm.; protein, 60 gm.; fat, 200 gm. and for the next four days the sugar excretion varied between 30 and 40 gm. daily. On July 19 the fasting blood sugar was 286 mg. On this day, without dietary change, he began to receive 15 cc. of a wheat bran extract daily, with the result that the sugar excretion immediately dropped to 12 to 15 gm. Increasing the dosage to 30 cc. daily produced no further lowering of the sugar excretion, while stopping the extract entirely after six days of administration allowed the sugar to mount again to around

30 gm. daily. On July 29, after four days of no vitamin administration, the fasting blood sugar was 200 mg. The regular vitamin extract, used on the other patients, was now administered daily in 10-cc. doses, and the urine at once became sugar-free. After five days of this extract administration the blood sugar was 143 mg. The urine remained sugar-free for two days after discontinuing the extract.

CASE VII.—M. H. S. (16415), a Chinese male, aged fifty-one years, was admitted to the hospital March 21, suffering from very large sloughing carbuncles of the back and neck. The diabetic condition was first discovered after his admission. He gave a history of nocturia, thirst, itchy skin and frequent boils and carbuncles for more than ten years. Insulin was used, as much as 100 units daily, for about three weeks, until the carbuncles were healing well. His course in the hospital was long, and the latter part is all we shall refer to. From June 3 to July 19 his diet was constant (carbohydrate, 40 gm.; protein, 50 gm.; fat, 180 gm.), but his blood sugar exhibited a tendency to rise, being 143 mg. on June 28, and 200 mg. on July 7. On July 14 he was given 15 cc. of the vitamin extract, repeated daily for five days. On July 18, the fasting blood sugar had fallen to 111 mg. and the patient was discharged.

Discussion. Of the cases here presented, numbers I, II, V, VI and VII present indisputable evidence of vitamin effect on sugar excretion, the third patient left the hospital just when the effects were beginning to be definite, and with the fourth the clinical improvement under vitamin treatment was very marked. In this case the presence of renal glycosuria complicated the picture.

From the results presented, one would roughly estimate 30 cc. of the vitamin solution to be equivalent to 30 units of insulin. In the first case 40 units of insulin were required to keep the patient aglycosuric, while 30 cc. of vitamin accomplished the same purpose. Likewise in the fourth case, on discontinuing the 30 units of insulin daily, 30 cc. of vitamin kept the sugar output at only a slightly higher level. In Case VI, 10 cc. of the extract stopped the excretion of 30 gm. of sugar. In Cases II, V and VI the patients promptly became sugar-free on the vitamin treatment. Case IV, V, VI and VII demonstrate the blood-sugar-lowering effect of the extract.

The increase in fever of the third case is typical of cases of active pulmonary tuberculosis treated with the vitamin. This initial fever increase, beginning usually on the second or third day of vitamin administration, soon subsides, however, and marked improvement begins. This phase of vitamin therapy will be reported later. It is felt that the results obtained warrant a thorough investigation of the influence of vitamin B on glucose utilization and storage, and a few preliminary results along this line are reported in the following paper.

No chemical studies of the active constituent of the vitamin solution have been made beyond the heating in alkaline solution which is claimed by Sherman and Burton[15] to destroy vitamin B almost completely. It is to be noted that in one instance (Case VI) an

extract made of fresh wheat bran alone was effective in lowering the sugar excretion.

We do not believe that these results point to diabetes being a deficiency disease any more than many other diseases due to lowered body vitality are deficiency diseases. We do feel, however, that such therapy as this affords an injured pancreas the best possible opportunity for functional recovery. Such treatment, in conjunction with insulin to rest the pancreas, might well produce striking results. In the fourth case presented, insulin and vitamin are seen to give better results than either alone.

Another important aspect of the use of this extract is that it is effective when taken orally, thus obviating the disagreeable and frequent injections necessary with insulin. Our work is yet too meager to permit us to say whether this material can replace insulin in many cases of diabetes, but the results indicate the value of further study of the question.

Summary. In the 7 cases of diabetes here reported evidence is offered of the effect of vitamin B in lowering sugar excretion.

Thirty cubic centimeters of the vitamin solution (an acid alcoholic extract of several plants) is estimated as roughly equivalent to 30 units of insulin.

Without pointing to diabetes as a deficiency disease, we believe that this therapy affords the injured pancreas an opportunity for functional recovery and might in combination with insulin give better results than either would alone.

It has the added advantage of oral administration and may be taken at home by patients to whom insulin could not be entrusted.

Addenum.—On August 5, 1927, there came to Peking journals containing abstracts of papers read by Dr. Frederick M. Allen dealing with work similar to ours. Since his results agree so closely with ours as set forth in this and the accompanying paper we desire to state here that this paper was mailed to another American medical journal on June 13, 1927, and was refused publication by it, July 18. Since Dr. Allen's publication antedates our own, we serve to confirm his results although we were not aware of his results until August 5, 1927.

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EFFECTS ON CARBOHYDRATE METABOLISM OF AN ACID–ALCOHOLIC EXTRACT OF PLANTS RICH IN VITAMIN B.

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After demonstrating the tendency of a vitamin-rich plant extract to correct sugar metabolism in diabetes, as recorded in the preceding paper,[1] we proceeded to test its physiologic properties in a variety of ways. We wished particularly to find its site of action in stabilizing the sugar metabolism, and whether it was of the nature of a plant insulin, such as Collip[2] had described under the term "glucokinin."

1. **Reduction of Glycosuria and Hyperglycemia in Diabetes.** This phase of its action has been demonstrated in the preceding paper regarding its clinical use.

2. **Effect on Normal Blood Sugar.** Four healthy adult rabbits were fasted for two days and then each injected with 2 cc. of the neutralized extract from which the alcohol had been evaporated. Sugar determinations on blood taken just before, and one, four and twenty-four hours after the injections, showed no significant change. The author also took 15 cc. orally after a fourteen-hour fast, and found the blood sugar to be unaffected four hours later. A great variety of nondiabetic patients have taken the extract orally without evidence of hypoglycemic reactions. We have not yet tested the effect on the blood sugar curve in the glucose tolerance test.

Apparently the extract does not lower the blood sugar below normal.

3. **Effect on Glycosuria and Hyperglycemia in Depancreatized Dogs.** Two healthy dogs were observed during a three weeks' period to be certain of normal blood-sugar value and freedom from glycosuria. They were then totally depancreatized.

Dog 1. July 23, totally depancreatized. Sugar excretion began within twenty-four hours.

July 27, fasting blood sugar was 176 mg. per 100 cc.

July 28, fasting blood sugar was 182 mg. per 100 cc.

Given 15 cc. vitamin extract by stomach tube at 5.30 P.M., and fed fifteen minutes later. At 10 P.M. blood-sugar was 512 mg.

July 29, fasting blood sugar at 10 A.M. was 256 mg. Very slight urine secretion, but 16 per cent glucose present. Again given 15 cc. vitamin extract. Appetite poor.

August 1, fasting blood sugar, 345 mg. Urine sugar about 12 per cent.

August 3, fasting blood sugar, 348 mg. At 10 A.M. 10 units insulin injected and 45 gm. glucose given by stomach tube at 3 P.M.

August 4, fasting blood sugar, 100 mg.

August 15, fasting blood sugar, 410 mg. at 2.30 P.M. 10 units of insulin injected at 2.30 P.M. Blood sugar at 5.30 P.M., 67 mg.

August 16, fasting blood sugar, 266 mg. at 9 A.M. 5 cc. vitamin extract by stomach tube at 9 A.M. Blood sugar 296 mg. at 12 M. 10 units of insulin injected at 12 M. Blood sugar 52 mg. at 4 P.M.

August 17, autopsy showed entire lack of pancreatic tissue.

Dog 2. Depancreatized July 29. Sugar excretion was established the next day. The same treatment was carried out as was given Dog 1, and the results were in all ways so similar that repetition is useless. Complete absence of pancreatic tissue was ascertained at autopsy.

From the data presented here, it is evident that the extract has no power to lower the blood-sugar level in depancreatized dogs. Indeed, by the disturbance it creates in the dogs, it seems actually to cause a rise in sugar. We cannot explain the suppression of urine observed. It is to be noted that sugar excretion continued however.

In these dogs insulin is seen to be very effective in reducing the hyperglycemia.

Finally, in order to see if the extract acted as a co-enzyme for insulin in the animals, we gave insulin alone one day, and the next day vitamin, followed by insulin. It is seen that the effect of the insulin the second day is practically identical with that of the preceding day.

From the results obtained on these dogs it is evident that the extract possesses no insulin-like action, nor is it capable of reinforcing the action of insulin in any way.

4. **Glycogen Storage in the Liver of Rabbits.** Seven half-grown rabbits were placed on a diet of black beans and mixed green vegetables. The composition of the diet was kept constant for all the rabbits, but the amount varied with the appetite of the animals. It was noticed that those receiving the vitamin as indicated below consumed more food and were more lively than the controls.

Four of the rabbits were killed after being on the diet for two weeks, the livers were quickly removed and glycogen content determined by the method of Pflüger.[3] The other three received 2 cc. of the vitamin extract by mouth for two weeks and then a similar amount by subcutaneous injection for another week. Before being injected, it was freed of alcohol and neutralized. At the end of this treatment these rabbits were killed and the liver glycogen determined in similar manner.

The glycogen content of the livers in the first group was as follows:

Rabbit 1—1.4 per cent; 2—0 (echinococcus cysts found in liver); 3—0 (echinococcus cysts found in liver); 4—0.63 per cent.

The figures for the second group were:

Rabbit 1—2.98 per cent; 2—3.04 per cent; 3—2.52 per cent.

There is thus a very definite increase in liver glycogen under vitamin treatment.

Summary and Conclusions. Discussion of Results. The extract we have used in this work seems to possess an action different from that of the yeast extracts used by other workers, since in no instance have we found it producing a hypoglycemia. It is without effect on the normal fasting blood sugar, but reduces the hyperglycemia of human diabetes. It increases glycogen storage in the liver. That it has no insulin-like action, however, is demonstrated by its entire lack of effect in depancreatized dogs. Nor does it enhance insulin action in such dogs. The conclusion seems evident, then, that its effect is exerted directly on the pancreas, but whether as a metabolic stimulant or as a source of supply of an insulin precursor is impossible to say. We do not believe that it acts directly to induce glycogen storage as insulin does, and as Collip suggests for his "glucokinin," but that this action is likewise secondary to its pancreatic effect.

We are at present engaged in obtaining a purified product of higher potency and in further studying its manner of action, especially as to whether the results by injection differ from those obtained when it is given *per os*.

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THE DUODENAL FLORA IN ACHLORHYDRIA.

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Our study of the flora of the duodenum in achlorhydria gastrica was undertaken with the object of finding out what effect the mere absence of hydrochloric acid in the stomach would have on the nature of the microörganisms in that part of the small intestine.

We were prompted to undertake this study because of the grad-

ually accumulating evidence pointing to the importance of achlorhydria in the etiology of pernicious anemia. Our old conception of pernicious anemia as a "blood disease," of unknown origin, has been changed to our present conception of it as a symptom complex, which is a result of a slowly acting hemolytic toxin of gastrointestinal origin.

We thought that, should we find in the duodena of achlorhydria patients hemolytic microörganisms, such findings might shed additional light on the etiology of pernicious anemia. An interesting fact concerning the etiology of pernicious anemia, brought to light within the last decade, is its familial occurrence. However, a recent paper by Dorst[1] compels one to think that it is really the achlorhydria and not the pernicious anemia that constitutes the familial characteristic, the anemia being merely a secondary development. Or, to put it in Dorst's words: "We feel so strongly that achlorhydria gastrica is a sign of grave clinical importance that we believe that every patient presenting this condition should be regarded as a potential case of Addison's anemia."

An interesting experience of one of us (L. R.) would seem to lend support to Dorst's statement. In 1918, he discovered achlorhydria in 3 patients of his, members of the same family, mother and two daughters. Six years after their achlorhydria was first discovered, the older of the achlorhydric daughters developed a glossitis, which was soon followed by the appearance of the typical symptoms of pernicious anemia and of a blood picture closely resembling the pernicious anemia type; while the mother and the second daughter are still presenting the condition of achlorhydria with only a moderate anemia of the chlorotic type.

As a full review of the literature dealing with the importance of achlorhydria as an etiologic factor in pernicious anemia has been already published in the works of Hurst,[2] Faber[3] and others, it is unnecessary for us to include such a review in this paper. It seems desirable, however, to refer briefly to some of the work done in recent years on the general subject of the bacterial flora of the duodenum in health and disease.

Special interest was attracted to this subject early in the present century. Cushing and Livingood[4] (1900) and Kohlbrugge[5] (1901) reported the duodenum practically sterile in the healthy individual during interdigestive periods. The former called attention to the rarity of infections following gunshot wounds in which the duodenum was perforated, whereas at lower levels such perforations were generally followed by peritonitis. Gessner[6] (1889), on the other hand, reported the presence of numerous staphylococci and streptococci in the duodenum.

With the advent of the method of duodenal drainage by means of the Einhorn technique, a new impetus was given to the study of the normal and pathologic flora of the upper intestinal tract. The

method was early applied with considerable success to the diagnosis of typhoid fever, and more particularly to the recognition of the typhoid carrier whose focus of infection with this organism was in the gall bladder. It is obvious that insofar as the object of the method was to recognize such specific disease germs as the typhoid and paratyphoid bacilli, the question of whether the withdrawn duodenal contents were contaminated with mouth and stomach organisms remained of slight importance. When, however, the method was applied to the determination of the normal duodenal flora and the types of organisms present in diseases of such nonspecific etiology as gall-bladder infections, achylia gastrica, gastric and duodenal ulcers and so forth, it is obvious that this question was of the very first importance. Hess[7] (1912), and MacNeal and Chace[8] (1913) were of the opinion that it was possible to get uncontaminated specimens of duodenal contents in this way. The latter authors attempted to prevent contaminating the samples with the mouth bacteria by covering the end of the tube with gelatin. This closed the entrance of the tube until the digestion of the gelatin by the gastric secretions. More recent authors have used a similar technique, employing salol instead of gelatin. The former is not removed until it comes into contact with the alkaline secretions of the duodenum. The majority of authors, however, have considered it unnecessary to take these elaborate precautions, believing that the time necessary for passing the tube to the duodenum permits the adjustment of the characteristic flora, especially when the tube is swallowed at the end of a ten- to twelve-hour fasting period. Some have favored an attempt at reducing the mouth flora by prolonged rinsing of the mouth with H_2O_2 just before taking the tube. Others have seen no value in this procedure. It should be stated here also that some experimenters have discarded the entire method of duodenal culturing as being untrustworthy. Boardman[9] (1924) found the bacteria of the duodenum as determined by this method to be indistinguishable from those of the mouth and stomach and concluded that it was impossible to obtain samples of duodenal fluid uncontaminated from these sources.

It appears to the present authors that the most convincing argument in favor of the reliability of the tube method of determining the nature of the duodenal flora is to be found in the fact that of the very considerable number of investigators who have used it, the majority report the normal healthy duodenum to be either quite sterile or quite poor in bacteria. On the other hand, there has been reported repeatedly a relatively rich duodenal flora in many pathologic conditions of the intestinal tract and its appendages. It is true that the types of bacteria seen in pathologic conditions by various observers do not differ qualitatively from those observed from time to time in normal individuals. The significant fact is the altered quantitative relationships in the different diseased states.

Before any logical deductions can be made regarding the richness

of the duodenal flora under pathologic conditions, it would be desirable to arrive at some conclusions with respect to the causes of the paucity of bacteria in the duodenum under normal conditions. In this connection the relation of gastric acidity has received considerable attention. Here there exists some difference of opinion. Hoefert[10] (1921) found a rich flora in most cases of achylia gastrica even when uncomplicated with other pathologic conditions, and expressed the opinion that the duodenal flora was to a large extent determined by the acidity of the gastric contents. In achylia and in hypoacidity cases he found Bacillus coli, Streptococcus fecalis (enterococcus), hemolytic and nonhemolytic staphylococci and streptococci as well as Bacillus proteus and other organisms. He states that in these cases the stomach and the duodenal flora were identical. Gorke[11] (1922) believes that gastric acidity and the state of the motor function of the stomach are the factors which determine the character of the duodenal organisms. In hyperacidity, he found the duodenum always sterile, while in hypoacidity and anacidity he always encountered an abundant flora. In the latter, Bacillus coli, enterococci and Gram-positive rods and Gram-negative cocci were the prevailing types. It is interesting to note that Gorke remarked the absence of typical mouth streptococci. Van der Reis[12] (1922) also reports heavy infections of the duodenum in hypoacidity, while hyperacidity cases and normals gave practically sterile cultures in his hands.

Some authors deny that gastric acidity is the chief controlling factor in the determination of duodenal infection. Raue[13] (1924) reports cases of cholecystitis and cholangitis in which repeated tests showed in the same person persistent heavy infections with Bacillus coli in spite of an abnormally high free-acid content in the stomach. Bogendörfer[14] (1925) is of the same opinion and extracted from the duodenal mucosa certain substances to which he gave the name "bacteriostanins" which were bactericidal for such organisms as enterococci, Bacillus coli, staphylococci and streptococci. He holds these "bacteriostanins" responsible for the normal bacteria-free condition of the duodenum. Lowenberg[15] (1926) considers the free hydrochloric acid of the stomach as only one factor, the least important, in his opinion, having to do with the determination of the nature of the duodenal flora. He has found the normal duodenal secretions themselves highly germicidal for many of the bacteria present under abnormal conditions and claims that this normal bactericidal power is lost in most of the conditions which are accompanied by the presence of a greatly augmented duodenal flora. That the bile itself is a factor of little importance in controlling this flora is sufficiently well established since normal bile is not only not bacteriostatic or bactericidal for most bacteria, but actually furnishes an available source of nutriment for many of them. Pneumococci and certain streptococci are exceptions to this statement.

The pathologic conditions giving rise to an increased bacterial flora at the duodenal level of the small intestine are various. Among them have been reported, in addition to idiopathic achylia gastrica, such conditions as gastric and duodenal ulcer, malignancies involving the intestinal tract, appendicitis and colitis. With respect to only two groups of diseases, however, does there seem to be practically universal agreement as to the relationship between the pathologic condition and the enriched duodenal flora. These are the diseases of the gall bladder and ducts and pernicious anemia. Special interest naturally attaches to the latter disease because of the obscurity surrounding its etiology. Practically every author who has determined the duodenal flora in cases of pernicious anemia has reported the finding of abnormal numbers of organisms in the fluid removed with the duodenal tube. Qualitatively the organisms belong to many types, some characteristic of the normal flora at lower level and others suggesting their origin in the mouth. One is especially struck with the regularity with which Bacillus coli is found in this condition as compared to its occurrence in other morbid states, giving rise to an increased bacterial growth in the duodenum. Hoefert[10] (1921), Gorke[11] (1922), Seyderhelm[16] (1923) and Goldman[17] (1924) call special attention to the heavy infections with Bacillus coli in pernicious anemia, and Weilbauer[18] (1922) contrasts its relatively frequent appearance in ulcer and biliary disease. All of these authors encountered hemolytic and nonhemolytic strains of Bacillus coli, while Seyderhelm claimed to have extracted anemia-producing substances from strains that could not be demonstrated to hemolyse *in vitro*. Lowenberg demonstrated the failure of the normal bactericidal power of the duodenal contents in all his cases of pernicious anemia and considers the enriched flora as the result of an ascending infection from the colon. He believes the accompanying achylia gastrica to be entirely subordinate to the loss in bactericidal power of the duodenal fluid as a cause of the augmented bacterial growth.

The material for our study consisted of 30 patients who presented the condition of persistent achlorhydria. Two of these suffered from pernicious anemia; 26 had anemia of the chlorotic type, with different degrees of severity, and only 4 gave a fairly normal blood picture.*

Method of Investigation. The duodenal contents were obtained in the following manner: The patients were instructed to present themselves at the office at 8.30 A.M., after a fourteen-hour fast.

* Since this paper was submitted an interesting case of familial occurrence of achlorhydria has come under the observation of one of us (L. R.). The interesting feature of this particular case is that two brothers of the same family died of pernicious anemia, while a third member, a forty-year old trained nurse, who was recently examined by us, was found to be suffering from achlorhydria.

TABLE I.—BACTERIOLOGIC FINDINGS IN THE DUODENAL CONTENTS IN CASES OF ACHLORHYDRIA.

Patient. No.	Name.	Date af taking specimen.	Hemoglobin, per cent.	Bacteriologic findings.*
1.	Mr. A. H.	3/15/26	64	Strep. viridans, B. coli (slightly hemolytic)
2.	Mrs. F. B.–1	5/15/26	44	Strep. hemolyticus, Strep. nonhemolyticus, B. coli (nonhemolyticus)
	" –2	6/ 8/26	44	Strep. viridans, B. coli (hemolytic)
	" –3	6/24/26	44	B. alkaligenes, Strep. viridans (mitis); Strep. nonhemolyticus
3.	Mrs. C. P.	1/15/26	83	Strep. viridans (salivarius), Gram-negative rods (nonhemolytic)
	"	3/15/26	83	Gram-negative rod (very hemolytic)
4.	Mr. O. N.	1/18/26	96	Strep. hemolyticus (A) pneumococcus; Non-lactose fermenting Gram-negative bacillus
5.	Miss F. B.	1/29/26	90	Strep. nonhemolyticus, B. coli (nonhemolytic)
6.	Mrs. E. P. L.–1	3/20/26	58	Strep. hemolyticus, Strep. viridans, B. coli (hemolytic)
	" –2	4/13/26	58	B. coli (hemolytic), slimy Gram-negative bacillus
7.	Mrs. L. B.	2/10/26	40	Gram-negative cocci
8.	Mrs. M. D.	3/27/26	50	B. coli (hemolytic)
9.	Miss J. L.	6/17/26	62	Strep. fecalis (enteroccus), B. coli, (hemolytic), Staph. albus, Gram-positive bacillus (non-hemolytic), B. coli (hemolytic), Strep. viridans, Staph. albus, diphtheroid, B. alkaligenes
10.	Mrs. G. G.	6/18/26	75	Several hemolytic organisms
11.	Mrs. M. H.	8/28/26	80	Strep. viridans, Staph. aureus (hemolytic), pneumococcus, yeast
12.	Mr. L. C.	6/21/26	75	B. alkaligenes, nonhemolytic rods
13.	Mrs. A. W.	7/12/26	75	B. coli (hemolytic), yeast
14.	Mr. W. S.	8/ 1/26	80	Strep. viridans, sarcinæ, yeast
15.	Miss I. B.	9/22/26	90	Strep. viridans, B. alkaligenes, yeast
16.	Mr. O. S.	10/ 8/26	70	Strep. hemolyticus, B. proteus, yeast
17.	Mr. L. de L.	10/16/27	77	Gram-positive hemolyticus bacillus, Strep. hemolyticus
18.	Mrs. D. B.	12/ 6/26	75	Strep. viridans, Staph. aureus (hemolytic), yeast
	"	8/21/26	75	Strep. viridans, B. alkaligines, Staph. albus, molds
19.	Miss A. T.	12/18/26	87	Strep. hemolyticus, Strep. viridans
20.	Mr. O. S.	12/27/26	75	B. coli hemolyticus, Strep. nonhemolyticus, pneumococcus
21.	Mr. A. K.	12/28/26	90	Pneumococcus, Staph. aureus (hemolytic)
22.	Mrs. L. B.	5/26/27	85	Strep. viridans, Gram-negative coccus (hemolytic, Strep. hemolytic B.
23.	Mrs. J. A. W.	2/ 1/27	90	Strep. viridans, nonhemolytic bacilli
24.	Mr. F. R.	7/ 9/27	90	Pneumococci, B. alkaligenes, Gram-negative coccus
25.	Mrs. A. M.	10/11/27	45	Strep. viridans, Gram-negative cocci, Staph. aureus (hemolytic)
26.	Mrs. C. A.	10/14/27	55	Pneumococcus, Micr. catarrhalis, diphtheroid, Gram-negative bacilli
27.	Miss L. J.	10/18/27	62	Pneumococcus, Gram-negative bacilli, Staph. aureus (hemolytic)
28.	Mrs. J. W.	10/20/27	83	Strep. viridans, Gram-negative cocci, Staph. albus
29.	Mr. J. A.	10/28/27	80	Strep. viridans, Gram-negative cocci, Staph. albus
30.	Mrs. F. R.	11/ 7/27	87	Strep. viridans, B. coli, Staph. albus

* No quantitative estimation of bacteria was made in this study, but this list includes only those organisms represented by a considerable number of colonies on the plates.

Prior to passing the duodenal tube, the teeth were thoroughly brushed and the mouth repeatedly washed and the throat gargled with a $\frac{1}{2000}$ solution of potassium permanganate. A sterile duodenal tube (Jutte's modification) was then passed into the stomach up to the pylorus mark. To stimulate peristalsis, 10 to 12 ounces of sterile water were then swallowed. The patient was placed on a couch on his right side and allowed to remain in that position from thirty to forty minutes, when the position of the duodenal tip was determined by fluoroscopic examination. After assuring ourselves by the fluoroscope that the tip was in the duodenum, the contents of the duodenum were withdrawn by means of a sterile Luer syringe, transferred to a sterile tube and placed in the icebox until sent to the laboratory for examination.

As a control, we made a bacteriologic study of the duodenal contents of 15 persons whose gastric contents showed a normal or a higher than normal percentage of hydrochloric acid. The method of obtaining the duodenal contents in the control group was exactly the same as in the achlorhydria group.

The bacteriologic examination consisted in plating several loopfuls of the material at once on freshly made blood agar, incubating at 37° C. for twenty-four to forty-eight hours and identifying the organisms as nearly as was required by the nature of the problem. Colonies that caused a change in the hemoglobin of the blood were accurately identified, as were others of a pathogenic nature. Those obviously belonging to saprophytic species were recorded only as Gram-negative bacilli, Gram-positive cocci, and so forth, unless belonging to easily recognized species.

In Table I are recorded the findings in specimens from achlorhydric patients. Table II gives the results of the examination of the duodenal contents of persons having normal gastric acidity. In Table I is recorded also the per cent hemoglobin of the patient about the time the duodenal specimen was taken, and in Table II the gastric hydrochloric acid as well as total acidity is shown. It should be noted that the figures 1, 2, and so forth following the symbol denoting the patient, refers to the first or second specimen respectively from the same patient.

Discussion. The most striking fact brought out in these tables is that the duodenal contents of all of our 15 normals (Table II) were entirely free from any organisms except those having well-known aciduric properties, while the achlorhydric patients (Table I) without exception gave a duodenal flora rich in nonaciduric organisms. This fact was even more striking when examining the plates than appears in the table, for it was the common observation that plates made from the achlorhydric specimens were covered with colonies, while the others, when not entirely free of colonies, generally showed only a very few, often but one or two large white colonies of yeast, or the easily recognized molds.

TABLE II.—BACTERIOLOGIC FINDINGS IN THE DUODENAL CONTENTS IN CASES WITH NORMAL AND ABOVE—NORMAL PERCENTAGE OF HYDROCHLORIC ACID.

Patient. No.	Name.	Date of taking specimen.	Gastric HCl in N/10 NaOH.	Total acidity in N/10 NaOH.	Bacteriologic findings.
1.	Mr. C. P. (duodenal ulcer)	4/16/26	65	75	Molds—yeast
2.	Mr. F. L. E.	4/16/26	90	100	Molds—yeast
3.	Mr G. B. (duodenal ulcer)	5/10/26	35	60	Molds—yeast
4.	Mr. A. P.	5/27/26	70	75	No growth
5.	Miss L. B.	10/ 1/26	20	30	No growth
6.	Mr. L. deL.	10/ 1/26	65	70	No growth
7.	Mr. C. L. P.	9/17/26	80	90	Yeast
8.	Miss E. S. (cholecystitis)	9/28/26	37	45	Yeast
9.	Mrs. E. C.	10/ 5/26	35	45	No growth
10.	Miss M. D.	10/19/26	44	55	Yeast
11.	Mr. A. H.	11/ 2/26	30	40	No growth
12.	Mr. A. A.	12/22/26	40	50	Yeast
13.	Mr. J. W.	12/23/26	95	110	No growth
14.	Mr. A. B.	11/ 2/27	60	70	No growth
15.	Mr. C. H. (duodenal ulcer)	11/16/27	70	85	No growth

Regarding the nature of the organisms found in the specimens from achlorhydric patients, one is struck at once with the frequency of appearance of species having blood-destroying qualities, both those giving on blood-agar plates well-defined zones of hemolysis, such as Streptococcus hemolyticus, hemolytic staphylococci and certain strains of Bacillus coli, and those giving on the plates only a green coloration as Streptococcus viridans and pneumococci. The fact that Bacillus coli and Bacillus alkaligenes and other Gram-negative bacilli frequently appear indicates that the flora of the duodenum does not all come from the mouth and throat and suggests the possibility of some abnormal condition in the secretions of the duodenum itself, as claimed by Lowenberg[15] (1926).

The significance of our findings becomes more apparent since Koessler[19] and his coworkers have demonstrated the effect of avitaminosis (especially the lack of vitamin A) on the permeability of the mucosa of the upper intestinal tract. In the presence of such a permeability, whether due to avitaminosis or to a duodenitis of any other origin, the baneful effect of a duodenal fluora rich in the hemolytic bacteria on the red blood cells should be considered and should be looked upon as a possible factor in the etiology of pernicious anemia.

It is noteworthy that out of the 30 cases of achlorhydria shown in Table I, 8 (23 per cent) suffered from anemia; 2 of these anemic patients were of the Addisonian type and 6 of the chlorotic type.

It is also interesting to observe (Table II) that the presence of such pathologic conditions as duodenal ulcer and cholecystitis did

not prevent the contents of the duodenum from being sterile as long as the hydrochloric acid in the stomach was sufficiently high to insure such sterility.

Conclusion. The duodenal flora of 45 persons was examined. Thirty of these had an achlorhydria, and 15, used as controls, had either a normal or above—normal content of hydrochloric acid in the stomach. Whereas the duodenal contents of the normals were practically sterile, those of the achlorhydric patients were rich in bacteria, many of which possess blood-destroying properties.

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SUSPENDERS VS. BELTS IN TREATMENT OF GASTRIC AND DUODENAL ULCERS.

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The practice of loosening one's belt to relieve pressure or fullness in the epigastric region has always been quite prevalent. This and many other instances gave me reason to suspect that the influence of wearing a belt in gastroenterologic disturbances is not a trivial one. In addition, the frequent complaints voiced to me by patients suffering from gastric or duodenal ulcers who attributed their discomfort to the wearing of a belt stimulated my interest in this problem and I determined to investigate whether the wearing of a belt caused any appreciable differences in the condition of male patients suffering from gastric or duodenal ulcers.

The investigation was conducted along the following lines: Forty male patients between the ages of twenty and forty, all of whom had a previous history of the same complaint extending from a few months to five years and over 80 per cent of whom were not engaged in manual labor, were selected. Every one of these patients had duodenal ulcer except No. 7 (Group I) and No. 14 (Group II), who had gastric ulcers, as verified both by a clinical and a Roentgen ray examination. All those selected were ambulatory patients undergoing the same treatment of special diet, special alkaline powders and other measures used in such cases. These 40 patients were divided into two groups of 20 each. Group I consisted of those who wore suspenders during the period of observation. Group II was composed of those whom I directed to wear belts.

Case Abstracts. Group I. Suspenders. 1.—L. K., aged thirty-eight years. Gastric complaint for three years. Recurrences every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two to three hours after meals, relieved by food and bicarbonate of soda. Night pain at about 2 or 3 A.M. Heartburn. Sour eructations. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. No six-hour residue. *Results:* All symptoms disappeared within one week. Discomfort in the epigastric region disappeared during the second week. *Follow-up:* Was under observation for two and a half years and reported every spring and fall. Feels well and made no complaint of recurrence.

2.—J. P. R., aged thirty-five years. Gastric complaint for four to five years with recurrences every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. No night pain. Heartburn. Sour eructations. No vomiting. *Roentgen ray findings:* Persistent defect in inner and outer border of duodenal bulb. Small gastric residue after six hours. *Results:* All gastric complaint disappeared within one week. Discomfort in epigastric region disappeared during the second week. *Follow-up:* Was under observation for two years and had no recurrences.

3.—I. S., aged forty years. Gastric complaint for four to five years, with recurrences every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. No night pain. Heartburn. Sour eructations. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared within one week. Raw feeling and discomfort in epigastric region disappeared in second week. *Follow-up:* Was under observation for two and a half years. Had recurrence after year and a half.

4.—C. M., aged twenty years. Gastric complaint for two months. No previous hospital medical treatment for ulcer. *Symptoms:* Heartburn. Sour eructations. No night pain. No vomiting. *Roentgen ray findings:* Persistent defect on outer border of duodenal bulb. No six-hours gastric residue. *Results:* Symptoms disappeared within one week as did the discomfort in the epigastric region. *Follow-up:* Under observation for two years and had no recurrence.

5.—A. R., aged twenty-one years. Gastric complaint for one year. Had one hospital treatment for bleeding duodenal ulcer one year before reporting. *Symptoms:* Pain, one and a half hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. Sour eructations. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared during the first week. Discomfort in epigastric region disappeared during the second week. *Follow-up:* Under observation for two and a half years. No recurrences.

6.—A. L., aged thirty-six years. Gastric complaint for three months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one and a half hours after meals, relieved by food and bicarbonate of soda. Heartburn. Sour eructations. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared during first week. Discomfort in epigastric region disappeared in second week. *Follow-up:* Under observation for two years. No recurrences.

7.—M. F., aged twenty-five years. Gastric complaint for six weeks. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one hour after meals, relieved by bicarbonate of soda. Night pain. Sour eructations. No heartburn. Intermittent vomiting spells. *Roentgen ray findings:* Penetrating gastric ulcer. *Results:* Symptoms disappeared in one week. Discomfort in epigastric region disappeared within ten days. *Follow-up:* Under observation for three years. Penetration disappeared. No recurrences.

8.—M. S., aged thirty-six years. Gastric complaint for two months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two to three hours after meals, relieved by bicarbonate of soda. Night pain. Heartburn. Sour eructations. No vomiting. *Roentgen ray findings:* Persistent defect of inner and outer borders of duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared in one week. Discomfort in epigastric region disappeared during second week. *Follow-up:* Under observation for three years. Recurrence after two years.

9.—J. G., aged thirty-five years. Gastric complaint for one year, recurring every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Sour eructations. No heartburn.

Roentgen ray findings: Persistent defect of inner and outer borders of duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared in one week. Discomfort in epigastric region disappeared during second week. *Follow-up:* Under observation for two and a half years. No recurrences.

10.—T. W., aged twenty-five years. Gastric complaint for six months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one and a half hours after meals, relieved by food and bicarbonate of soda. Heartburn. Sour eructations. Intermittent vomiting spells. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared in one week. Discomfort in epigastric region disappeared in two weeks. *Follow-up:* Under observation for two and a half years. No recurrence.

11.—I. M., aged thirty-eight years. Gastric complaint for three months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. Night pain. Occasional vomiting. No heartburn. Sour eructations. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms and discomfort in epigastric region disappeared within one week. *Follow-up:* Under observation for two years. Recurrences at the end of twelve and twenty-four months.

12.—J. A., aged thirty-three years. Gastric complaint for four years; recurrences every year during the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. *Roentgen ray findings:* Persistent defect of inner and outer border of duodenal bulb. Small six-hour gastric residue. *Results:* Symptoms disappeared in one week. Discomfort in epigastric region disappeared in second week week. *Follow-up:* Under observation for two and a half years. Recurrence at end of one year.

13.—A. W., aged thirty-seven years. Gastric complaint for three years; recurrences every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one and a half hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. Sour eructations. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared in second week as did the discomfort in the epigastric regiln. *Follow-up:* Under observation for two and a half years. Had recurrence after one year.

14.—W. C., aged thirty-one years. Gastric complaint for four months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. Sour eructations. *Roentgen ray findings:* Persistent defect of inner and outer borders of duodenal bulb. No six-hour gastric residue. *Results:* Pain and discomfort in epigastric region disappeared in one week. *Follow-up:* Under observation for two and a half years. No recurrences.

15. J. C., aged thirty-six years. Gastric complaint for one and a half years; recurrences during the spring. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one and a half hours after meals, relieved by food. No night pain. Heartburn. Sour eructations. Intermittent vomiting. *Roentgen ray findings:* Irregular duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared during first

week. Discomfort in epigastric region disappeared in second week. *Follow-up:* Under observation for two and a half years. No recurrences.

16.—H. K., aged thirty-five years. Gastric complaint for five years; recurrences at intervals of two years, during the spring. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Constant night pain. Heartburn. Sour eructations. *Roentgen ray findings:* Irregular duodenal bulb. No six-hour gastric residue. *Results:* Symptoms and discomfort in epigastric region disappeared in one week. *Follow-up:* Under observation for two and a half years. No recurrences.

17.—R. M., aged thirty-two years. Gastric complaint for four years; recurrences every six months, in spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms and pain disappeared in one week. Discomfort in epigastric region disappeared in second week. *Follow-up:* Under observation for two years. Recurrence after one year.

18.—A. F., aged thirty-eight years. Gastric complaint for two years; recurrences yearly during the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two and a half hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. Sour eructations. *Roentgen-ray findings:* Irregular duodenal bulb. Small six-hour gastric residue. *Results:* Symptoms and discomfort in epigastric region disappeared in one week. *Follow-up:* Under observation for two and a half years. No recurrences.

19.—I. S., aged twenty-five years. Gastric complaint for four months. No previous hospital medical treatment. *Symptoms:* Pain, two and a half hours after meals, relieved by food and bicarbonate of soda. Heartburn. Slight sour eructations. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms and discomfort in epigastric region disappeared in one week. *Follow-up:* Under observation for two years. No recurrences.

20.—M. R., aged thirty-five years. Gastric complaint for three months. No previous hospital medical treatment. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. No night pain. Heartburn. Sour eructations. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Pain and discomfort in epigastric region disappeared in one week. *Follow-up:* Under observation for two years. Recurrence after one and a half years.

Group II.—Belts. 1.—I. C., aged thirty-five years. Gastric complaint for four years, recurrences every two years in the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. Sour eructations. Intermittent vomiting spells. *Roentgen ray findings:* Persistent defect of inner border of duodenal bulb. Small six-hour gastric residue. *Results:* Symptoms disappeared in second week. Discomfort in the epigastric region disappeared at the end of the seventh week. *Follow-up:* Under observation for two and a half years. Recurrences at the end of twelve months and twenty-four months.

2.—J. S., aged twenty-one years. Gastric complaint for one and a half years. No previous hospital medical treatment for ulcer. Recurrences in spring and fall. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Heartburn. Sour eructations. Night pain. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared at end of the second week. Discomfort in the epigastric region disappeared at the end of the sixth week. *Follow-up:* Under observation for two years. Recurrence (in the fall) at the end of one year.

3.—M. B., aged thirty-seven years. Gastric complaint for two years. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. *Roentgen ray findings:* Persistent defect of inner and outer borders of the duodenal bulb. Small six-hour gastric residue. *Results:* Symptoms disappeared after two weeks. Discomfort in the epigastric region disappeared after seventh week. *Follow-up:* Under observation for two and a half years. Recurrences at the end of twelve and twenty-four months.

4.—M. H., aged twenty-eight years. Gastric complaint for four years; recurrences yearly, in the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. Night pain. No heartburn. Sour eructations. Occasional vomiting. *Roentgen ray findings:* Persistent defect of the inner and outer borders of the duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared after one week. Discomfort in the epigastric region disappeared after the fifth week. *Follow-up:* Under observation for two years. Recurrence after one year.

5.—S. S., aged thirty-one years. Gastric complaint for five years; recurrences yearly at the beginning and then every six months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. No night pain. Slight heartburn. No vomiting. *Roentgen ray findings:* Incomplete filling of the duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared after first week. Discomfort in the epigastric region disappeared after the fifth week. *Follow-up:* Under observation for two and a half years. No recurrences.

6.—D. Z., aged twenty-five years. Gastric complaint for two years; recurrences yearly in the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one hour after meals, relieved by rest and food. Night pain. Sour eructations. Slight heartburn. *Roentgen ray findings:* Persistent defect of the outer border of the duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared after one week. Discomfort in the epigastric region disappeared after the fifth week. *Follow-up:* Under observation for two years. No recurrences.

7.—S. C., aged thirty-three years. Gastric complaint for four years; recurrences yearly at first and then every six months, mostly in the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. No night pain. Heartburn. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared after one week. Discomfort in the epigastric region disappeared after the fifth week. *Follow-up:* Under observation for two years. Recurrence after year and a half.

8.—M. S., aged forty years. Gastric complaint for three years; recurrences every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one and a half hours after meals, relieved by food and bicarbonate of soda. Night pain. Heartburn. Sour eructations. Intermittent vomiting. *Roentgen-ray findings:* Defect of the inner border of the duodenal bulb. Small six-hour gastric residue. Visceroptosis. *Results:* Symptoms disappeared after two weeks. Discomfort in the epigastric region disappeared after the fifth week. *Follow-up:* Under observation for three years. First recurrence after eighteen months and then every six months. Changed to suspenders.

9.—I. G., aged twenty-nine years. Gastric complaint for eight months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. Heartburn. Sour eructations. No night pain. No vomiting. *Roentgen ray findings:* Persistent defect of the inner and outer borders of the duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared in one week. Discomfort in the epigastric region disappeared after four weeks. *Follow-up:* Under observation for two and a half years. Recurrence in year and a half.

10.—S. M., aged thirty-five years. First interval of relief three years, when he had a hemorrhage for which he had hospital medical treatment. Another interval of relief for two years. Recurrence in the fall. *Symptoms:* Pain, two and a half hours after meals, relieved by food and rest. No night pain. Slight sour eructations. No heartburn. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared in two weeks. Discomfort in the epigastric region disappeared at the end of the fourth week. *Follow-up:* Under observation for three years. Recurrences yearly in the fall.

11.—S. K., aged thirty-seven years. Gastric complaint for one year. No previous hospital medical treatment. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Night pain. Occasional vomiting. *Roentgen ray findings:* Persistent defect on the inner and outer borders of the duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared in one week. Discomfort in the epigastric region disappeared at the end of the fourth week. *Follow-up:* Under observation for one and a half years. Recurrence after one year.

12.—D. D., aged thirty-five years. Gastric complaint for six months. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one hour after meals, relieved by vomiting. Heartburn. Sour eructations. Night pain. Vomiting. *Roentgen ray findings:* Irregular duodenal bulb. Small six-hour gastric residue. *Results:* Symptoms disappeared after one week. Discomfort in the epigastric region disappeared during the fourth week. *Follow-up:* Under observation for three years. Recurrence after one year.

13.—A. R., aged thirty-one years. Gastric complaint for one year. One previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. No vomiting. No heartburn. No sour eructations. *Roentgen-ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared after first week and discomfort in the epigastric region disappeared during the fourth week. *Follow-up:* Under observation for one and a half years. No recurrences.

14.—(Gastric ulcer.) I. C., aged thirty-eight years. Gastric complaint for two years, recurrences in the fall. No previous hospital medical treat-

ment. *Symptoms:* Pain, one hour after meals, relieved by bicarbonate of soda and rest. Pain aggravated by heavy food. No night pain. Sour eructations. Heartburn. No vomiting. *Roentgen ray findings:* Deep constant incisura on large curvature of stomach. Pylorospasm. *Results:* Symptoms disappeared after two weeks. Discomfort in the epigastric region disappeared after the fifth week. *Follow-up:* Under observation for three years. Recurrences at end of first and second years.

15.—J. S., aged twenty-six years. Gastric complaint; recurrences in the fall, over period of one and a half years. No previous hospital medical treatment. *Symptoms:* Pain, three hours after meals, relieved by food and bicarbonate of soda. No night pain. Sour eructations. Heartburn. Belching. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared during first week. Discomfort in the epigastric region disappeared after fourth week. *Follow-up:* Under observation for two years. No recurrences.

16.—H. G., aged thirty-eight years. Gastric complaint for five years; recurrences every six months, spring and fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two and a half hours after meals, relieved by food and bicarbonate of soda. No night pain. Heartburn. Sour eructations. Belching. No vomiting. *Roentgen ray findings:* Irregular duodenal bulb. No six-hour gastric residue. *Results:* Symptoms disappeared after two weeks. Discomfort in the epigastric region disappeared during the fifth week. *Follow-up:* Under observation for two and a half years. Recurrences after six months and eighteen months. Changed to suspenders.

17.—P. L., aged forty years. Gastric complaint for two years; recurrences yearly in the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, three hours after meals, relieved by food and belching. Sour eructations. Heartburn. No vomiting. Night pain. Belching. *Roentgen ray findings:* Irregular duodenal bulb. Minimum six-hour gastric residue. *Results:* Symptoms disappeared after two weeks. Discomfort in the epigastric region disappeared after five weeks. *Follow-up:* Under observation for two years. Recurrence after one year.

18.—J. W., aged thirty-five years. Gastric complaint for one year, especially in fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain at night only. No heartburn. No sour eructations. Occasional vomiting. *Roentgen ray findings:* Persistent defect of inner and outer borders of duodenal bulb. Minimum six-hour gastric residue. *Results:* Symptoms disappeared after one week. Discomfort in epigastric region disappeared after four weeks. *Follow-up:* Under observation for two years. Recurrence after one year.

19.—H. F., aged twenty-five years. Gastric complaint for four years; recurrences every two years in the winter. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, two hours after meals, relieved by food and bicarbonate of soda. Night pain. No heartburn. No sour eructations. No vomiting. Belching. *Roentgen ray findings:* Irregular duodenal bulb. *Results:* Symptoms disappeared after one week. Discomfort in the epigastric region disappeared after third week. *Follow-up:* Under observation for two years. No recurrences.

20.—B. L., aged forty years. Gastric complaint for two years; recurrences yearly, in the fall. No previous hospital medical treatment for ulcer. *Symptoms:* Pain, one hour after meals, relieved by food and hot water bag. Night pain. Heartburn. Sour eructations. Belching. Occasional

vomiting. *Roentgen ray findings:* Defect of the inner and outer borders of the duodenal bulb. No six-hour gastric residue. *Results:* Symptoms

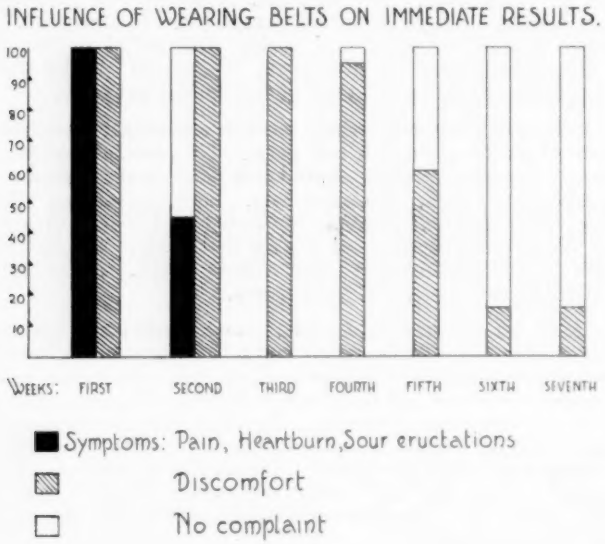

FIG. 1.

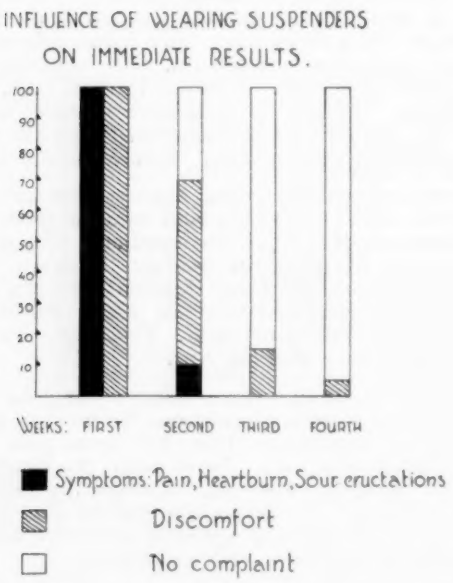

FIG. 2.

disappeared after two weeks. Discomfort in the epigastric region disappeared after fourth week. *Follow-up:* Under observation for two years. Recurrences after six to eighteen months.

Influence of Wearing a Belt on Immediate Results. In this study I laid particular stress in ascertaining the difference, if any, in the two groups as to the time required for the disappearance of the symptoms and the discomfort in the epigastric region. Thus, as as illustrated in Fig. 1, I noted that for the first week the symptoms, such as pain, heartburn, sour eructations, vomiting, belching and so forth, were present in all the cases. At the end of the second week all but 45 per cent of the cases reported the disappearance of the symptoms, but it was not until the third week had passed that all the cases were clear in this respect. The discomfort in the epigastric region, which the patients described to me as a "raw feeling," required a longer period of time for its complete elimination.

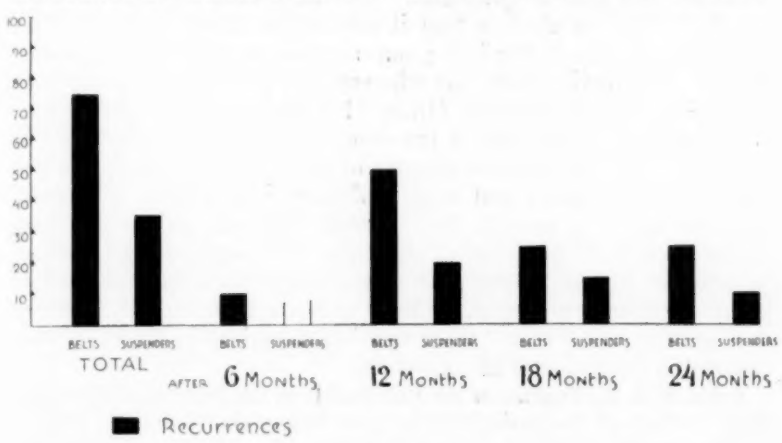

FIG. 3.

Thus, for the first four weeks it was present in practically 100 per cent of the cases. By the end of the fifth week there was a marked decrease, so that all but 60 per cent of the patients in this group were free from that feeling. However, it was not until the seventh week of treatment had passed that this discomfort was eliminated in all the cases.

Influence of Suspenders on Immediate Results. On the whole, the symptoms and discomfort in the epigastric region were eliminated more quickly in this, the suspender group, than in the previous group, which wore belts. As shown in Fig. 2, the second week found but 10 per cent of the patients still affected with the above-described symptoms, while at the end of the third week all the patients reported that they were no longer troubled with them. Discomfort in the epigastric region was reported by but 60 per cent of the patients in the second week, and this number was gradually decreased during the succeeding two weeks, so that at the end

of the fourth week of treatment all the cases were clear in this respect.

Influence of Belts and Suspenders on Remote Results. I was also anxious to determine from this study whether or not the wearing of suspenders in preference to a belt had any effect upon the remote results in the treatment of cases of gastric or duodenal ulcer. The patients were required to report to me twice a year, in the spring and in the fall, irrespective of whether or not they had suffered recurrences. The results of the observations made during this follow-up period are embraced in Fig. 3. Thus I found that in the group which wore belts (Group II) 75 per cent of the patients had suffered recurrences, while in the group that was directed to wear suspenders only 35 per cent of the patients suffered a repetition of their gastric complaint. This difference is rendered more striking when we observe that it means that there were twice as many recurrences in the belt group as there were in the suspender group. Fig. 3 will show that whereas Group I had no recurrences during the first six months, Group II during the same period had recurrences in 10 per cent of the cases. The same illustration will also show that the greatest amount of recurrences are found at the end of the first year, and here, too, there is a striking difference between the two groups, for, whereas the belt group (II) had recurrences in 50 per cent of the cases, the suspender group had recurrences in but 20 per cent of the cases. Another interesting point of difference is that, while 5 patients in Group II suffered two or more recurrences, there was but 1 patient in Group I who reported a repetition of his complaint.

Relation of the Position of the Belt Buckle to the Pylorus or Duodenal Bulb.—Since all the patients wore belts before the treatment began, a fluoroscopic study was made to determine the relation of the position of the belt buckle to that of the pylorus or duodenum. I found that in 60 per cent of the cases the belt buckle was situated directly over the pylorus and to the left of the duodenum. In about 15 per cent of the cases the buckle was located right on the duodenal bulb and in the remainder of the cases it was situated just below the pyloric region of the stomach.

Conclusions. Upon the basis of the above findings, I am convinced that in the treatment of patients suffering from gastric or duodenal ulcer it is of definite advantage to have the patient wear suspenders in place of a belt. Not only is such a change advisable in the treatment of ambulatory patients suffering from gastric or duodenal ulcer, but it should also be made in the postmedical treatment of those who were under the hospital care for such disturbances.

EMPTYING OF THE GALL BLADDER WITH ESPECIAL REFERENCE TO THE USE OF PITUITRIN.

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Kalk and Schondube[1] first suggested that the gall bladder could be emptied of its contents by the subcutaneous use of pituitary extract. If this drug was efficacious, it could replace the Lyon-Meltzer method of drainage of the gall bladder by the use of the duodenal tube and instillation of magnesium sulphate, obviating inconvenience to the patient in carrying out this procedure for therapeutic purposes.

Kalk and Schondube[1] base their conclusions largely on data obtained by the use of the duodenal tube. In their experience, the drug is very efficacious in emptying the normal gall bladder, so much so that they base their "pituitrin test" on its efficacy; if no B bile flows from the tube after administration of pituitrin, they conclude that the biliary tract is abnormal. They point out that the drug may also be efficacious in causing some emptying of the pathologic gall bladder, and use it to combat atony and biliary stasis, and in selected cases of biliary obstruction due to stone. Pribram, Grunenberg and Strauss[2] demonstrated the action of pituitary extract on the gall bladder by the cholecystographic method. The plate accompanying their article shows the gall bladder shadow to be two-thirds the size of the shadow apparent previous to the injection of pituitary extract, but they state that there is a secondary enlargement of the gall bladder shadow, with some decrease in opacity. They advise using pituitrin injections as a preliminary procedure in roentgenographing the gall bladder, to insure the gall bladder being empty previous to the injection of the dye. Kaznelson and Reimann[3] gave pituitary extract in 3 cases with a visualized gall-bladder shadow and so caused a flaccid pear-shaped shadow to become oval and smaller, which they interpret as due to the contraction of the gall-bladder wall. In none of their cases, however, was there disappearance of the shadow following the injection. Chiray, Lebon and Callegari[4] point out that pituitary extract gives a more rapid and more lasting effect on the biliary flow than magnesium sulphate. Copher and Kodama[5] observed in dogs after intravenous injection of pituitary extract an immediate relaxation of the duodenum and a great fall in the common-duct pressure, however there is a secondary quick increase in the tonus and activity of the intestine.

With the idea of evaluating the action of pituitary extract, and

comparing its advantages and disadvantages with the more commonly accepted procedures, this work was undertaken. Two methods were used: The duodenal tube and the cholecystogram.

I. Duodenal-tube Data. A series of 43 patients were successfully intubated fifty-eight times, some of the patients being intubated two or three times for check-up purposes. When the flow of bile had been established, the bile was collected in bottles until a definite color was obtained in several successive bottles. When the color of the bile coming through the tube was constant, a stimulant was used. After a period of forty-five to sixty minutes, if the gall bladder was not emptied by the first stimulant, as shown by the failure to obtain a dark or B bile, a second stimulant was used. If again no B bile was obtained, a third stimulant was used. If the third stimulant was likewise unsuccessful, the tube was withdrawn, and the experiments recorded as "no stimulant efficacious." If the first stimulant produced a flow of B bile, further stimulation was not used. The fluid coming through the tube was graded as to depth of color by the naked eye as having a bile concentration of 1 to 4. One represents a light-yellow bile as obtained in the first partition of a normal drainage, 2 is a deep yellow, 3 in a yellowish-brown or light brown, and 4 represents the dark brown, almost black, B bile. An attempt to grade the depths of color by the use of arbitrary standards was found to be somewhat unsatisfactory, as the colors are often difficult to match. An attempt was also made to grade the biles by estimating the quantity of dye pigment after the method of van den Bergh, as suggested by Kalk and Schondube, but the variable dilution factors interfered, such as the dilution by gastric and intestinal juices, dilution by the magnesium sulphate solution used as a stimulant, interference by olive oil, and the like. The naked-eye estimation was found practical. In cholecystomectized cases no bile stronger than II was obtained, whereas in normal cases the bile was usually graded as IV.

The average duration of the 58 drainages was two hours and forty-seven minutes. The average number of stimulants used was 2.3. Three stimulants were especially compared: Surgical pituitrin (Parke, Davis & Co.) 1 cc. injected subcutaneously, warm magnesium sulphate, 50 per cent strength, repeating the stimulation by frequent flushing of the papilla of Vater through the tube, and a single injection of 1 ounce of warm olive oil. In isolated cases, hot water, epinephrin hydrochlorid 1 to 1000, 1 cc. injected subcutaneously, and atropin sulphate $\frac{1}{100}$ gr. injected subcutaneously, were used. As a rule the pituitrin was the first stimulant used, as it was thought desirable to ascertain if magnesium sulphate or olive oil could empty the gall bladder if pituitrin failed.

Pituitrin was used for stimulation in 53 of the 58 drainages (see Table I). In 27 cases with a normal biliary tract, no B bile was

TABLE I.—ANALYSIS OF 53 DRAINAGES, SHOWING ACTION OF PITUITRIN

	Normal cases.	Pathologic cases.	Total.
Pituitrin caused flow of B bile	9	3	12
Pituitrin failed to cause flow of B bile, with subsequent drainage by other stimulants	11	5	16
Pituitrin failed to cause flow of B bile, as did all other stimulants	7	18	25
Total number of cases in which pituitrin was used	27	26	53

obtained in 7 cases by the use of any stimulant. In the remaining 20 cases, pituitrin caused stimulation in 9, or 45 per cent, but in the remaining 11 cases, or 55 per cent, there was a flow of B bile after pituitrin had failed, by the use of magnesium sulphate or olive oil. Considering all the cases, both normal and pathologic, in which pituitrin was used, that is, 53 cases, a response to some stimulant was obtained in 28 cases. Of these 28 cases, 12 were stimulated by pituitrin, or 43 per cent, and in the remaining 16, or 57 per cent, some other stimulant as magnesium sulphate or olive oil was efficacious after the pituitrin had failed. The above figures show pituitrin to be an ineffective stimulant, as more than half of the gall bladders could be emptied by other stimulants after pituitrin had failed.

Pituitrin not only failed to empty the gall bladder in many cases, but it actually stopped or slowed the flow in 9 of the 53 cases, or 17 per cent. In 2 of these cases, the stoppage of flow was followed in a short interval by the appearance of B bile. In 6 cases there was no B bile subsequent to the slowing of flow, but B bile was obtained by the use of magnesium sulphate or olive oil after a wait of one hour. In the remaining case, the pituitrin caused a marked slowing of flow, but with no B bile after any kind of stimulation. In 3 of the above 9 cases, the patients complained bitterly of abdominal cramps and had bowel movements during the course of the drainage. These data are given as justification for the dosage of pituitrin used, 1 cc. of surgical pituitrin. Kalk and Schondube used 2 cc. of the same preparation, which may account for some of the discrepancies. They also noted in 6 of their cases a primary decreased flow of bile after pituitrin injection. In the cases observed by the cholecystographic methods to be reported below, it was again noted that frequently the injection of 1 cc. of pituitrin caused abdominal cramps, but not necessarily with emptying of the gall bladder.

An analysis of Table II demonstrates that reliance cannot be placed on any one stimulant in drawing conclusions from a drainage. Thus it is apparent that in 3 cases where magnesium sulphate was used unsuccessfully, pituitrin caused the appearance of B bile, while conversely magnesium sulphate caused a B bile to appear eight times where pituitrin had previously been unsuccessful. Again,

olive oil caused emptying in 1 case where pituitrin previously failed, 1 case where magnesium sulphate previously failed, and 4 cases where both pituitrin and magnesium sulphate had previously failed. The duodenal drainage is, therefore, not complete in the absence of any of these three stimulants. From a therapeutic point of view, the use of olive oil is indispensable.

TABLE II.—SHOWING NUMBER OF SUCCESSFUL STIMULATIONS BY ONE REAGENT, PREVIOUS TO WHICH THERE HAD BEEN UNSUCCESSFUL STIMULATIONS BY OTHER REAGENTS.

	Total of successful stimulations.	Pituitrin failed previously.	Magnesium sulphate failed previously.	Olive oil failed previously.	Both other two stimulants failed previously.
Pituitrin . . .	12	"	3	0	0
Magnesium sulphate	13	8	"	1	2
Olive oil	6	1	1	"	4

Moreover, the 7 cases where no B bile was obtained despite all types of stimulation, where subsequent drainage was normal, or the Roentgen ray showed a normal gall-bladder shadow, or both, illustrate that a single drainage in which no B bile is obtained does not prove that the biliary tract is pathologic. For example, a case of duodenal ulcer had three successive drainages, the first two eliciting no B bile, but dark bile being obtained from the third on pituitrin stimulation. Failure of the normal biliary tract to deliver B bile may be due to errors in technique, such as failure of the tube to be opposite the papilla; it may be due to the fact that the gall bladder may have emptied itself by psychic reflex at the sight of food, as shown by Elman and McMaster;[6] it may be due to the fact that the gall bladder may have emptied itself due to the mechanical manipulation of the passage of the tube, as shown by Hamrick.[7] Moreover, Boyden[8] has shown that the gall bladder may empty independently of digestive processes through stimulation of the sympathetic nervous system, or by superficial cutaneous injuries as shaving and skin incisions, even when both adrenals have been removed. A single duodenal drainage, if no B bile is obtained, is no more to be relied on than a single oral cholecystography if the gall bladder is not visualized.

II. Cholecystographic Data. A number of patients were used to detemine the relative stimulating power of pituitrin and a fat meal. The usual procedure consisted in giving the dye by mouth the evening before. The next day plates were taken at 11.00 A.M. If a shadow was present the patient was given an injection of 1 cc. of surgical pituitrin and second and third plates were then taken at half-hour intervals. The patient was then given a fat meal and a fourth plate taken two hours later. The fat meal used is that suggested by Brooks[9] and consists of two soft boiled eggs, two slices

of bread well buttered, and a glass of half milk and half cream. It thus contains all the important fat stimulants as emphasized by Boyden.

The gall bladders of 28 patients were visualized, 23 of these having a normal biliary tract, 3 were recovering from catarrhal jaundice and 2 were gall-stone cases. The results are tabulated in Table III. In only 4 cases was there any reduction of appreciable degree

TABLE III.—SHOWING EFFECT OF 1 CC. OF PITUITRIN ON GALL-BLADDER SHADOW.

	Cases.
Reduction in size of shadow	4 (14 per cent)
Shadow larger or more dense a half hour after injection	15 (54 per cent)
No change in size of shadow	9 (32 per cent)

in the size of the gall-bladder shadow, and in more than half the cases there was a larger or more dense shadow a half hour after the injection of pituitrin. The fat meal, however, used following the pituitrin injection caused marked diminution in size or disappearance of the shadow in 20 of the 28 cases, or 70 per cent.

It is pertinent to this discussion to demonstrate that the action of pituitrin as shown above clinically is in accordance with the physiologic data at our disposal. There has been considerable discussion as to whether the gall bladder empties by the contractile power of its wall, or is merely a passive elastic organ emptied by the relaxation of the tonus of the duodenal wall. Whitaker[10] has completely summarized all the data in this regard. The gall bladder fills, however, only when the duct is closed, as it has been shown that the gall bladder will not fill if the duct is kept open with a cannula (Winkelstein and Aschner[11]), and that no gall-bladder shadow can be visualized following the injection of dye if the ducts are open (Copher[12]). The action of pituitrin as a smooth-muscle stimulant is well known. There is a slight amount of smooth muscle in the wall of the gall bladder, which would tend to cause emptying, and a large amount of smooth muscle in the duodenal wall surrounding the distal end of the common duct, contraction of which would prevent emptying and cause filling. The predominant effect of pituitrin, therefore, is constriction at the outlet of the common duct. This was borne out clinically by the frequent stoppage of flow of bile through the tube and the better visualization of the gall-bladder shadow shown in the roentgenogram following the use of this drug. The minority of cases in which the gall bladder partially emptied on administration of pituitrin can be explained as due to the peristalsis of the duodenum caused by the injection of pituitrin. It has been shown by Burget[13] and by Copher[12] that bile will flow out during the relaxation of the duodenal wall caused by the negative phase of the peristaltic wave.

Summary. Clinically, the use of surgical pituitrin in 1-cc. doses usually fails to empty the gall bladder, as judged by data obtained both with the duodenal tube and oral cholecystography. It stops the flow of bile in an appreciable number of cases and may aid in the visualization of the gall bladder. It is markedly inferior to fat in emptying the gall bladder.

The results of duodenal drainage, using magnesium sulphate, olive oil and pituitrin are compared. The use of olive oil (or some other form of fat) is indispensable.

A single drainage with failure to obtain B bile is of no diagnostic significance.

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REVIEWS.

OSLER'S MODERN MEDICINE. Reëdited by THOMAS MCCRAE, M.D., Professor of Medicine, Jefferson Medical College, Philadelphia, assisted by ELMER H. FUNK, M.D., Assistant Professor of Medicine, Jefferson Medical College, Philadelphia. Third edition. Pp. 948; 82 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $9.00.

VOLUME V includes a section on Diseases of the Blood, with chapters on the general pathology of the blood-forming organs, pernicious and secondary anemia, chlorosis and leukemia, purpura and hemophilia, diseases of the spleen, and a new chapter on transfusion of blood. The section on Diseases of the Lymphatic System has chapters on the diseases of the lymphatic glands and Hodgkin's disease. Then follow sections on the Diseases of the Ductless Glands, Diseases of the Urinary System, Vasomotor and Trophic Disorders (including Raynaud's disease, angioneurotic edema, diffuse scleroderma and erythromelalgia) and Diseases of the Locomotor System (chapters on myositis, myotonia congenita, myotonia atrophica, amyotonia congenita, arthritis deformans, osteomalacia, achondroplasia, pulmonary osteoarthropathy, Paget's disease and others).

The articles continue the high standard of excellence and thoroughness of revision set in the preceding volumes. The majority of chapters are written by contributors to former editions and show the result of their widened experience. New contributors have been well selected. R. K.

PRACTICAL THERAPEUTICS. By HOBART AMORY HARE, B.Sc., M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College of Philadelphia. Twentieth edition. Pp. 1094; 166 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $7.50.

A WORK that has reached its twentieth edition needs no review. Suffice it to say that it has been brought thoroughly up to date. Newly included are only such therapeutic agents whose merits have been well proven. R. K.

BLOOD PRESSURE. ITS CLINICAL APPLICATIONS. By GEORGE WILLIAM NORRIS, A.B., M.D., Professor of Clinical Medicine in the University of Pennsylvania; HENRY CUTHBERT BAZETT, M.B., B.Ch. (OXON.), F.R.C.S. (ENG.), Professor of Physiology in the University of Pennsylvania, and THOMAS M. MCMILLAN, A.B., M.D., Assistant Physician to the Pennsylvania Hospital, Cardiologist to the Philadelphia General Hospital. Fourth edition, thoroughly revised. Pp. 387; 48 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $4.50.

A COMPLETE revision has brought this well-known work quite up to date. The first two chapters, which are new and comprise nearly a fourth of the book, are of particular interest: an excellent and detailed discussion of the physiologic considerations of blood pressure. The many new references throughout the book are ample evidence of the thoroughness with which the authors have carried out their task. This new edition should find many new friends among general and special practitioners alike. R. K.

ALLGEMEINE UND EXPERIMENTELLE PATHOLOGIE. By DR. HERMANN PFEIFFER, Professor of General and Experimental Pathology, University of Graz. Pp. 649; 64 illustrations. Berlin: Urban and Schwarzenberg, 1927.

IT takes more than a casual knowledge of German medicine to understand the significance of the title of this book, and in fact an unfortunate latitude of definition of the term may be said to exist in Germany today. An abstract rather than a mixture of abstract and criticism is, therefore, perhaps the most useful service the reviewer can offer in this short space.

System pathology, of course, does not appear; general pathology in the sense of the pathologic anatomy of the degenerations, neoplasms and so forth also is mostly absent. After a short introduction on concepts and general factors in disease, the external causes of disease (physical, chemical, bacteriological and animal) are considered in approximately 150 pages. Inflammation occupies the next 20 pages; fever, 20; immunity, 40. Disturbances of the blood receive 30 pages; the circulation, 50; respiration, 15; metabolism, almost 100; the glands of internal secretion, over 100; experimental tumor research, the final 30—truly a remarkable distribution to American eyes. The book compares favorably, however, with Hering's, and Lüdke's and Schlayer's *Pathologische Physiologie* though for completeness one must turn to the older Krehl and Marchand, and for a one-volume work, Tendeloo's *Allgemeine Pathologie* is preferable in several particulars. E. K.

DIE MENSCHENTHYMUS IN GESUNDHEIT UND KRANKHEIT, TEIL I, DAS NORMALE ORGAN. By J. AUG. HAMMAR, O. Professor der Universität Upsala. Pp. 570; 350 illustrations and 64 tables. Leipzig: Akademische Verlagsgesellschaft, M. B. H., 1926.

THE thymus is one of the few structures of the mammalian body of which a knowledge of its function is still lacking. For over twenty years Professor Hammar has devoted himself to the study of the structure of this organ as it exhibits itself at all periods of its life history. He has now analyzed the vast amount of information he has accumulated, and in this supplementary volume to the *Zeitschrift für Mikroskipisch-Anatomische Forschung*, sixth volume, he presents the full account of the normal organ. It includes individual consideration of 345 cases, which cover the period from the third fetal month to the ninetieth year. In each case are given measurements of weight and size, with a low-power view showing relative amounts of cortex, medulla and interlobular connective tissue. Chapters are also devoted to a complete historical review, status thymicus, and the thymus in pregnancy. Professor Hammar's monograph constitutes the most authoritative source of information on the human thymus which has yet appeared. W. A.

HYPNOSIS. By PROF. PAUL SCHILDER, M.D., PH.D., and DR. OTTO KAUDERS, Assistant, of the Psychiatric Clinic, Vienna. Pp. 118. New York and Washington: Nervous and Mental Disease Publishing Company, 1927. Price, $2.50.

THE Viennese School pays more attention to hypnosis than do other medical centers, and this volume is no extravagant presentation of the subject. Psychoanalysis here finds abundant support. The importance of a "sleep center" in the vicinity of the third ventricle is commented upon. In discussing the nature of hypnosis, these writers insist that Charcot was wrong in his contention that hypnosis is an artificially induced hysteria. To them it is rather a primitive, archaic regression phenomenon. N. Y.

CHEMICAL TESTS. By RUSSELL C. ERB, B.S., M.S. Pp. 262. Easton, Pa.: The Chemical Publishing Company, 1927. Price, $3.00.

THIS volume consists of a compilation of qualitative tests in various fields of chemistry. The tests are stated briefly with no statement concerning the principles underlying them. No references are given. Such a volume may be of value in a clinical laboratory as a ready means of finding methods provided one is familiar with the fallacies of the tests. L. J.

BRONCHOSCOPY AND ESOPHAGOSCOPY. By CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S. Second edition. Pp. 457; 179 illustrations and 10 color plates. Philadelphia: W. B. Saunders Company, 1927. Price, $8.00.

IT seems superfluous to render a review on the endoscopic work of an author known literally the world over for his work in this particular field. Were one to hunt for an example of a true specialist he would find it in the writer of this work. This, the second edition, has been entirely reset and comprises tracheobronchoscopy, esophagoscopy and gastroscopy as well as peroral endoscopy. The uses of the endoscope have been so widened that at present it is used not only in every removal of foreign bodies from the lungs, trachea, stomach and so forth, but furnishes a great aid to the internist as well as the surgeon in diagnosis, prognosis and treatment. The perfection of this technique has done much toward preparing the way for a marked reduction in mortality in surgical diseases of the chest.

A work manual such as this is cannot include a historic presentation without a degree of bulk that would impair its readable usefulness. For that reason, little effort has been made to trace the course and fundamentals of the development of this most important subject. As presented to the reader this handy volume gives a concrete, concise and clear presentation of the basic and practical uses of this branch of science.

Aside from the great fund of knowledge found in these pages, the reading of the innumerable cases of phenomenal recovery leaves one aghast as to future possibilities in this line.

I cannot recommend the work too strongly. E. E.

CANCER CONTROL. Report of an International Symposium, held under Auspices of the American Society for the Control of Cancer, Lake Mohonk Conference, 1926. Pp. 336; 32 illustrations. Chicago: Surgical Publishing Company of Chicago, 1927.

THIS volume records the proceedings of an international congress of one hundred and nine physicians who met to discuss the control of cancer. In this group seven European countries were represented by sixteen eminent men. The crystalized opinions and experiences of the world's leading cancer specialists are presented in a group of twenty-seven addresses. Fifteen of these concern the organized campaign against cancer; eight relate to cancer research; only four deal with treatment. Frank discussions follow each address focusing attention upon the control of a rapidly increasing disease.

Surgeons, radiologists and research workers unite in productively supporting what appears to be an intelligently conducted world-wide crusade to control cancer. P. S.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME II: ADMINISTRATION AMERICAN EXPEDITIONARY FORCES. Prepared under the Direction of MAJOR-GENERAL M. W. IRELAND, SURGEON-GENERAL, and COLONEL JOSEPH H. FORD, M.C. Pp. 1123; 167 illustrations. Washington: United States Government Printing Office, 1927.

THIS volume considers certain of the more important administrative activities of the Medical Department in the American Expeditionary Forces during the World War. The volume is arranged in five sections: I. Organization and Administration of the Chief Surgeon's Office; II. Medical Activities of Territorial Sections; III. Hospitals; IV. Evacuation of Patients to the United States—Discontinuance of Hospitals; V. The Army of Occupation in Germany. J. S.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME XI: SURGERY. Prepared under the direction of MAJOR-GENERAL M. W. IRELAND, SURGEON-GENERAL. Pp. 1324; 620 illustrations. Washington: United States Government Printing Office, 1927.

THE three sections of this volume are devoted respectively to General Surgery, Orthopedic Surgery and Neurosurgery. A great amount of statistical data is presented. The volume is profusely illustrated and presents a very complete record of the developments in surgery, which have resulted from the experiences of the World War. The technique and results of treatment are recorded in a manner which should make this volume of especial value to students of surgery. J. S.

LOCAL IMMUNIZATION. By PROF. A. BESREDKA, Pasteur Institute, Paris. Edited and translated by DR. HARRY PLOTZ, Pasteur Institute, Paris. Pp. 181; no illustrations. Baltimore: The Williams & Wilkins Company, 1927. Price, $3.50.

IN this little volume the author presents certain observations based upon laboratory experiments, and to some extent upon epidemiological and clinical studies which support the theory of local immunization. The material is very clearly presented and the theory is elaborated in a most fascinating manner. The volume should prove especially useful in stimulating further work, since it presents many new leads for investigation of the puzzling phenomena of immunology. J. S.

A TEXTBOOK OF PATHOLOGY. By FRANCIS DELAFIELD, M.D., LL.D., Some-time Professor of the Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York; and T. MITCHELL PRUDDEN, M.D., LL.D., Some-time Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Revised by FRANCIS CARTER WOOD, M.D., Director of the Pathological Department, St. Luke's Hospital, New York, Director of the Institute of Cancer Research, Columbia University, New York. Fourteenth edition. Pp. 1339; 850 illustrations. New York: William Wood & Co., 1927. Price, $10.00.

IN this latest revision by Dr. Wood, "aside from many detailed changes, especially new bibliographic references, the question of vitamins and hormones has been touched upon, changes have been made in the chapters on diseases of the thyroid, pancreas, lungs and in that on the blood, while a consideration of some modifications in our conceptions of certain lesions of the liver and the gall-bladder have also been included. Additional matter has been inserted in the chapter on infectious diseases, in that dealing with the bones and joints and that on the nervous system. A considerable number of illustrations have been added. The chapter on lesions following various types of poisoning has been eliminated," also the chapter on preservation and staining of pathologic tissues. The method of making postmortem examinations has wisely been retained, and the valuable footnote references enlarged. In spite of the manifold important demands on the reviser, one cannot but express the hope that the next edition will be even more drastically brought up to date and that the numerous antiquated drawings will be replaced. E. K.

BOOKS RECEIVED.

New Books.

*Bedside Diagnosis.** By AMERICAN AUTHORS. Edited by GEORGE BLUMER, M.D. Three volumes and index. Pp. 2820; 890 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $30.00 a set.

The Endocrines in General Medicine. By W. LANGDON BROWN, M.A., M.D., F.R.C.P. Pp. 144. New York: Paul B. Hoeber, Inc., 1927. Price, $3.00. A very "brief account of the endocrine system and its diseases in a form . . . of service to the general practitioner" from the English point of view.

*The Measurement of Mental Capacities.** By CYRIL BURT, M.A., D.Sc. Pp. 52; 14 illustrations. London: Oliver & Boyd, 1927. Price, sixpence.

*Pernicious Anemia.** By BEAUMONT S. CORNELL, M.D. Pp. 311; 7 illustrations. Durham, North Carolina: Duke University Press, 1927. Price, $4.00.

*Organic Inheritance in Man.** By F. A. E. CREW, M.D., D.Sc., PH.D. Pp. 214. London: Oliver & Boyd, 1927. Price, 12/6.

*The Meningiomas.** By HARVEY CUSHING, C.B., D.S.M., A.M., M.D., LL.D. Pp. 53; 28 illustrations. Glasgow: Jackson, Wylie & Co., 1927. Price, 21s.

*Bacterial Vaccines and their Position in Therapeutics.** By LEONARD S. DUDGEON, C.M.C., C.B.E., F.R.C.P. (LOND.). Pp. 87. New York: Paul B. Hoeber, Inc., 1927. Price, $2.50.

*Max von Pettenkofer.** By EDGAR ERSKINE HUME. Pp. 142; 8 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, $1.50.

*Epidemic Influenza. A Survey.** By EDWIN O. JORDAN, PH.D., Sc.D. Pp. 599; 97 illustrations. Chicago: American Medical Association, 1927.

*Poliomyelitis. With Especial Reference to the Treatment.** By W. RUSSELL MACAUSLAND, M.D. Pp. 402; 173 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $5.50.

Methods and Problems of Medical Education (Eighth Series). Pp. 372; illustrated. New York: Division of Medical Education, Rockefeller Foundation, 1927.

Peking Union Medical College. Selected Contributions. Volume VI. Peking: Peking University Medical College Press, 1927.

Progressive Medicine, Volume IV, December, 1927. Pp. 340. Philadelphia: Lea & Febiger, 1927.

The Current Significance of the Word "Alum." By WILLIAM D. RICHARDSON. Pp. 93. Chicago: Commonwealth Press, 1927. Price, $1.00.

New Editions.

*Neoplastic Diseases.** By JAMES EWING, A.M., M.D., Sc.D. Third edition. Pp. 1127; 546 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $14.00.

*Pulmonary Tuberculosis, its Etiology and Treatment.** By DAVID C. MUTHU, M.D., M.R.C.S. Second edition. Pp. 381; 28 illustrations. New York: William Wood & Co., 1928. Price, $5.00.

*The Foundation of Health.** By WILLIAM BARNARD SHARP, S.M., M.D., PH.D. Second edition. Pp. 288; 19 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $2.50.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Pericardial Pain: An Experimental and Clinical Study.—It is pointed out by CAPPS (*Arch. Int. Med.*, 1927, **40**, 715) that there is a decided difference in opinion among clinicians and in the literature as to the rôle of pain in pericarditis. In order to investigate this point, the author took the opportunity in every case in which the pericardial sac was tapped to test the sensation of the parietal and visceral layers with a silver wire. This exploratory procedure failed to elicit pain when the serous membrane was touched with the wire. In addition to these clinicoexperimental studies, he also made a careful clinical investigation as to the occurrence of pain in dry pericarditis. He believes that pain itself is not of any particular moment as an indication of pericarditis—certainly the typical pain which we are wont to associate with inflammation of the serous membrane. Occasionally angina-like pains may be observed. If there is persistent pain it is believed that it is due to secondary involvement of the pleura. These observations will confirm the generally accepted view that during the course of coronary thrombosis a friction rub may appear, give absolutely no subjective symptoms and be recognized only objectively.

Bone Marrow as an Organ.—SABIN and DOAN (*Proc. Soc. Exper. Biol. and Med.*, 1927, **25**, 121) note that the structure of bone marrow is adapted to the maintenance of an erythroid-myeloid ratio, the regulation of the proportion of the stages of maturation of both red and white strains, and the delivery of cells to the blood, related in part by vascular and in part by chemical factors. The chemical factors are chemotactic and growth-stimulating. Nucleic acid is a well-known chemotactic factor. A maturation factor for erythrocytes has been discovered by Minot and Murphy in liver.

The Incidence of Scarlet Fever Streptococci in Throats of Diphtheria Patients.—Additional evidence is brought by RHOADS (*J. Infect. Dis.*, 1927, **41**, 377) to show that it is of extreme importance to isolate carefully individuals suffering from diphtheria who are in contagious disease wards. It is shown in this report that hemolytic streptococci were cultured from the throats and noses of 29 patients in a series of 100 who had the diagnosis of diphtheria. A little over 50 per cent of these strains of hemolytic streptococci were shown to be scarlet fever streptococci by the toxin neutralization method. It is suggested by the author that some of the diagnosed cases of diphtheria were in reality cases of scarlet fever which were diphtheria carriers and, furthermore, that these observations account for the development of the negative Dick test in the course of acute infections diagnosed culturally as diphtheria.

The Heart after Severe Diphtheria.—One of the most important complications of diphtheria from the point of view of prognosis, immediate and ultimate, is cardiac involvement. There are various explanations for the clinical syndrome associated with cardiac disturbance in the course of diphtheria, which vary from the idea held by some that it is due to a toxic myocarditis to the thoughts conveyed by other authors that this cardiac derangement is the result of injury to the cardiac nerves in which the myeline sheath is chiefly involved. Because of the frequency with which diphtheria is considered to leave permanent cardiac disabilities and, incidentally, because of the important etiologic information which must apparently come out of this study, JONES and WHITE (*Am. Heart J.*, 1927, **3**, 190) have investigated 100 young individuals who had severe diphtheria from five to eight years before the present examination. These individuals were studied in detail with especial reference to heart findings on physical examination, electrocardiographic tracings on all cases and Roentgen ray examination if there was a possible enlargement of the heart. Two patients only were found to have any trouble even suggestive of heart injury and in these patients the effect on the heart was apparently minimal.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Redundant Colon.—GAUSS (*Arch. Surg.*, 1927, **15**, 560) states that the redundant colon is one that is too long for its owner. It is congenital in origin. It is not materially influenced by the factors of age, sex or body habitus. It is an organic structure which develops func-

tional characteristics. Hence the symptoms may develop any time during the life of the patient. The chief symptoms are constipation, gas distress, abdominal pain and their attendant evils. The diagnosis is suggested by a history of malfunction of the colon and is confirmed by roentgenograms, which show the redundancy. Symptomatic redundant colon must be differentiated from chronic and atypical appendicitis from gall bladder disease and from other abdominal disorders. The treatment aims at the restoration of the function of the colon with the minimum of intervention. A high residue diet and lubrication, both by mouth and by rectum, are the basis of the treatment. Antispasmodics and sedatives are useful accessories. Surgical intervention has a place of minimum importance in the cycle of the redundant colon. Under proper medical care the great majority of persons with redundant colon promptly return to an approximate state of wellbeing.

The Treatment of Osteomyelitis. — ORR (*Surg., Gynec. and Obst.*, 1927, **45**, 446) declares that his earlier cases treated by the method of drainage and rest did so well, the care of the patients became so much easier and the end results were so satisfactory, that as time went on he was able to go further and further in lengthening the periods of immobilization and nondisturbance of the wound. Not only have very serious wounds healed without much treatment, but highly septic patients have recovered when recovery was not to be expected with ordinary treatment. Distribution of sepsis has certainly been reduced and body resistance to injection has certainly been fortified by this policy of what might be called "extreme rest." Patients with extensive contractures, deformities due to muscle spasm, have been put at rest in a few hours by very extensive inclusion of the body and extremities in plaster of Paris. The treatment of the wound both as to primary operation and as to secondary care has been reduced to almost nothing on the proposition that drainage and rest are the only factors of any particular importance.

Mesenteric Lymphadenitis.—BELL (*Surg., Gynec. and Obst.*, 1927, **45**, 465) claims that all cases of mesenteric lymphadenitis should be treated as tuberculous, until proved otherwise. All cases of suspected mesenteric lymphadenitis, either acute or chronic, should have an exploratory laparotomy, because of the various pathologic complications which may exist and the extreme danger of failure to diagnose acute appendicitis. Heliotherapy should be given for those patients who do not promptly respond to sunlight, rest and a high-caloric diet. Roentgen ray therapy is of great value in the acute form and in the chronic form, with acute exacerbations where there is marked glandular enlargement without caseation. Operative removal of glands should not be undertaken except for pathologic examination, unless the glands are caseous or are abscessed. The examination of the mesentery for enlarged glands should be a routine whenever the abdomen is opened. Tuberculous mesenteric glands are common in various stages of disease without symptoms. Activation is caused by environmental and hygienic conditions, physical exercise or intercurrent superimposed infections, which lower resistance to the invasion of tubercle bacilli.

Chronic Subdural Hematoma.—GRANT (*Ann. Surg.*, 1927, **86**, 425) declare that ingravescent subdural hemorrhage may follow an apparently extremely insignificant cranial trauma. The underlying pathology and predisposing causes of the condition are not clearly understood, although it seems possible to differentiate microscopically between the subdural clot following trauma and that consequent upon chronic systemic disease. Symptomatically the onset of intracranial pressure is insidious, with a rather abrupt development of localizing signs pointing to involvement of a definite cortical area. Exposure of the involved area by surgical means and evacuation of the clot is the proper treatment. Since such hemorrhage is frequently bilateral inspection of the contralateral dura is always indicated. If the postoperative course gives evidence of a return of intracranial pressure this is due either to general cerebral edema or an undiscovered contralateral clot. Lumbar puncture or reëlevation of the original flap does not seem to benefit the situation. Hypertonic solutions should be given a thorough trial.

Treatment of Empyema in Children by the Closed Method and Suction Drainage.—PARKER (*Boston Med. and Surg. J.*, 1927, **197**, 653) states that infants and young children whose resistance has been lowered by a previous pneumonic infection, do not stand well the added shock of general anesthesia and operation of any magnitude. The operative treatment of choice is that which can be performed painlessly under local anesthesia, with a simple shockless technique, which is consistent with adequate drainage. The use of chlorin solutions as frequent irrigations is a very important part of the treatment, not only on account of the antiseptic properties of the chlorin, but also on account of its solvent action on fibrin and pleural adhesions. The author describes a simple thorocostomy—closed in character—using a catheter with a rubber dam shield tied about it approximately 1½ to 2 inches from its tip. The low mortality rate and freedom from more than temporary complications obtained by this method justifies its serious consideration and further trial.

The Status of Enterostomy in the Treatment of Acute Ileus.—VAN BEUREN and SMITH (*Arch. Surg.*, 1927, **15**, 288) declare that enterostomy as a treatment for acute ileus has been used in only a small percentage of the total number of cases. It has apparently been reserved as a last resort in the cases in which the patient is the sickest and the condition is most advanced. There is evidence suggesting that this procedure has been effective in lowering the mortality rate, but it has apparently had little influence on the general mortality rate of all cases in a series. The actual value of enterostomy as a treatment for acute ileus, must be determined ultimately by statistical proof. Enterostomy is not a "sure cure," nor is there any magic about it. Like other surgical procedures it must be performed in the right way and at the right time to be effective. In cases in which the patient has acute ileus in an advanced stage, the condition is primarily chemical and purely mechanical treatment cannot be effective.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Asthma in Children.—PESHKIN and FINEMAN (*Am. J. Dis. Child.*, 1927, **34**, 815) call attention to the difference in their results and the reports in the literature. They say that the difference may have been due to the fact that the dry powders used by them were more concentrated, that the skin tests were properly performed and interpreted with both methods, and because the subjects tested were unselected groups of children. Ninety-one children with asthma and 9 with eczema, urticaria or angioneurotic edema, ranging in age from eight months to fourteen years, were tested by the scratch and intradermal methods with thirty-three corresponding proteins. Dry powder extracts (Wodehouse) were employed for the scratch and routine fluid extracts (Coca) for the intradermal tests. The fluid extracts were also employed for scratch test when the intradermal gave a reaction above the control. All of these children were under observation at least one year. In interpreting the reactions obtained with the scratch method, all reactions above the control were considered positive. With the intradermal method, although all reactions above the control were recorded, only reactions of 2+ or more were considered definitely positive. This interpretation is in accordance with accepted standards for this method. Reactions of 1+ should not be entirely ignored in spite of the fact they are most frequently nonspecific. Thirty-eight children of the entire series reacted negatively with the scratch method. With the intradermal method 15 children gave negative reactions and in 23 the reactions obtained were ± and 1+ only. Sixty-two children reacted positively to the scratch method. With the intradermal method 26 patients gave reactions not larger than 1+ and 36, 2 and 3+. No patients were encountered who gave definitely positive reactions with the scratch method. The total number of negative reactions obtained with the scratch method were 3032. The corresponding reactions with the intradermal method were definitely positive, 2 and 3+, in 0.53 per cent; 1+, in 4.15 per cent; negative, = and ± in 95.32 per cent. The total number of positive reactions, ± to 4+, obtained with the scratch method was 233. The corresponding reactions with the intradermal method were definitely positive in 19.31 per cent, 1+ in 27.47 per cent and negative in 53.22 per cent. Pseudoreactions or nonspecific reactions were common with the intradermal method. Practically all the ± and a majority of the 1+ reactions were of this character. The nonspecific reactions occurred most commonly with the following substances in their order of frequency: house dust, chicken meat, rice, wheat, chicken epithelium, tobacco, corn, pyretheum (an insecticide), goose and goat epithelium and lamb. Pseudoreactions with the scratch method were relatively infrequent. Four children gave a history of positive pollen reactions and negative ragweed reactions with both

methods of testing, and they gave positive reactions by the conjunctival test to the dry powder. This method has been shown by the authors to be rapid, safe and reliable in patients refractory to the skin test. General reactions occurred in 2 per cent of the patients tested with the intradermal method and in none with the scratch method. The scratch method was found to be superior to the intradermal test for the following substances: rabbit hair, horse dander, ragweed, cottonseed, duck and goose feathers, cat and dog hair, mustard and egg white. The intradermal test was superior to the scratch test for the following substances: house dust, chicken epithelium, chicken meat, wheat and corn. In the presence of negative scratch reactions to horse serum and goat hair the intradermal method, in a small percentage of the cases, will reveal definitely positive reactions. From the standpoint of safety and the determination of etiologic sensitizations, the scratch method would appear to be superior as a routine procedure for testing. The value of the intradermal method cannot be ignored, and one method should not be used to the exclusion of the other.

The Incidence of Rheumatism, Chorea and Heart Disease in Tonsillectomized Children.—KAISER (*J. Am. Med. Assn.*, 1927, **89**, 2239) made a survey of 48,000 school children, 20,000 of whom had had the tonsils removed and 28,000 who had not been operated upon. The history pertaining to rheumatic fever, chorea, scarlet fever and heart disease was obtained, and 1200 showing signs of rheumatic fever, chorea and heart disease were examined. Most of the 20,000 children had had their tonsils removed for a period of five years or more. Rheumatic fever, joint pains or growing pains occurred in both groups; 8 per cent of the tonsillectomized group and 10 per cent of the nontonsillectomized group had rheumatic manifestations. Many of the former had rheumatic symptoms before tonsillectomy. The tonsillectomized child not yet infected has a decidedly better chance to escape rheumatic infection over the same period of time than the nontonsillectomized child. Recurrent attacks of rheumatic fever were less common in the group in which the operation had been performed. Chorea occurred only slightly less often, 0.4 per cent as compared to 0.5 per cent, in the tonsillectomized group. The incidence of carditis following chorea was decidedly less in the tonsillectomized children. Scarlet fever occurred in 7.6 per cent of the tonsillectomized children, and in 16 per cent of the nontonsillectomized group. The children whose tonsils had been removed who developed scarlet fever developed considerably less valvular heart disease than those in the control group who developed scarlet fever. Rheumatic heart disease was found in 450 of the 20,000 tonsillectomized children and in 817 of the 28,000 who had not been operated upon. Many of the children in the former group developed heart disease before tonsil enucleation. A careful analysis of 478 cases of carditis showed that in 83 per cent the condition developed before the tonsil operation and in 17 per cent after the tonsillectomy. Based on a control study of 20,000 tonsillectomized children, the conclusion must be made that the tonsil is a factor in the etiology of rheumatism, scarlet fever and chronic heart disease. The child who has had his tonsils removed is assured a greater protection against those infections than the one in whom the tonsils remain.

Differential Diagnosis of Bone and Joint Tuberculosis in Childhood.—SIMON (*Arch. f. Kinderh.*, 1927, **82**, 157) reminds us that there is a group of diseases marked by pain on walking and on active and passive movement of the ankle or knee joint and also by some limitation of movement. At first these diseases, which have no definite name, are difficult to differentiate from tuberculosis, but after a time the symptoms disappear, and it is seen that they are not due to tuberculosis. In the infant with generalized syphilis there are usually manifestations in the skin or special organs, and the typical syphilitic osteochondritis of the infant is quite characteristic. With increasing age and as late syphilis develops, the diagnosis becomes more difficult. The Wassermann reaction does not always serve. Often tuberculosis and syphilis are both present in the bones. Syphilis seems more likely to appear in the diaphyses, while tuberculosis is more often seen in the epiphyses. There is occasionally a rare tuberculous infection of the diaphysis which is called osteomyelitis tuberculosa. In tuberculosis there is much swelling of the diaphysis, atrophy of the bone and the absence of periostitis. These points distinguish it from syphilis and also from the osteomyelitis produced by pyogenic bacteria. The location of preference in syphilis is the vault of the cranium and the framework of the nose, while tuberculosis most frequently attacks the bony border of the orbit or the lower jaw. In other parts of the body both diseases are likely to attack the same sites. The Roentgen ray of osteomyelitis with the massive new bone formations in irregular shapes and the lack of bone atrophy is characteristic. In chronic polyarthritis the deformities, mostly in the joints, are especially typical in the fingers and toes. The great number of joints involved is characteristic. In chronic arthritis deformans the Roentgen ray shows markedly changed epiphyses and moderate atrophy of disuse, which is never so severe as in tuberculosis with skeletal changes in the same degree. Tuberculous foci in the femur or acetabulum which have not broken through to the joint cause very slight symptoms of disease, and hence may not be at all suggestive of tuberculosis.

Physiologic Variations in the Leukocytes in Infants and in Children.—FLETCHER and MITCHELL (*Am. J. Dis. Child.*, 1927, **34**, 807) in a series of studies found that the times of day and night are factors to be considered in the evaluation of leukocyte counts in infants and children. They claim that blood counts must be done at the same time of day on successive days. Any variation which may be interpreted as a digestive leukocytosis is inconstant. As only 8 patients were studied it is not at all certain that these results will be substantiated with observation of larger groups of patients. It was found in these 8 patients that there was a fluctuation in the total leukocyte count in twenty-four hours, in which the higher counts occurred from about 2 to 4 in the afternoon and from 12 to 4 in the morning, and the lower counts from about 7 to 8 in the morning and from 7 to 10 in the evening. In young infants the curve of the lymphocytes followed the total leukocyte count closely. In older children the number of polymorphonuclear cells more nearly corresponded to the fluctuation in total counts. Both total and differential counts varied greatly in the course of twenty-four hours. In the case of the total leukocyte count the variation was as much as 175 per cent. The polymorphonuclear cells varied as much as 400 per cent and the lymphocytes, 250 per cent.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Bismuth in the Treatment of Syphilis.—Anwyl-Davies (*Lancet*, 1927, **1**, 148 and 199) gives a valuable review of the five years' life history of bismuth in the treatment of syphilis. It appears that bismuth salts do not kill the Spirocheta pallida *in vitro*, even when mixed with blood or blood serum; but if fresh cellular extract, such as rabbits' liver extract, is added the solution immediately becomes active and is able to destroy spirochetes. This bismuth-protein combination, Levaditi and Nicolau have designated as "bismoxyl." Levaditi, Gérard and Manin believe that bismuth has specific immunity-producing qualities more marked than those of any other antisyphilitic agent. Kolle found that insoluble bismuth salts would inhibit the development of chancres in rabbits even after one hundred and nine days, but that the easily absorbed soluble preparations do not have this inhibitory action. He does not consider that this prolonged inhibitory effect is due to a reservoir of deposited bismuth in the tissue. Kolle and Evers found that a bismuth deposit made subcutaneously in animals would inhibit the development of a primary lesion. They believe the effect to be due to an inhibition of tissue reaction rather than of spirochetal growth, because the animals in which the primary lesion was thus inhibited were found to have systemic infections transmissible by lymph node inoculation. The author's review next covers the absorption and elimination of bismuth, from which it appears that the metal is deposited in the large intestines, kidneys, spleen, salivary glands, brain and liver. The kidney, lung and spleen contain the largest amounts. There is no accumulation of the metal at the site of the syphilitic lesions. Renal irritation is apparently produced by the soluble but not the insoluble bismuth compounds (Levaditi). The routes of elimination of bismuth are identical with those of mercury. The drug has been found in the spinal fluid, although observers disagree on this point. Elimination of a single dose of an insoluble preparation such as bismuth salicylate occurs in about five days—77 to 92 per cent of it by way of the urine and 8 to 23 per cent in the feces. It appears that metallic bismuth is the best tolerated of all the bismuth preparations, the tartrate, for example, being tolerated only one-third as well and having a much sharper effect on the kidney. It has been indicated, too, by the work of Groehl and Myers that arsenic is much more rapidly eliminated in the urine when bismuth thiosulphate is given.

Choice of Preparation. Aqueous suspensions of bismuth hydroxid, bismuth oxychlorid, metallic bismuth and sodium potassium bismuth

tartrate are all in use. Bismuth oxychlorid and metallic bismuth are put up with chloretone in an isotonic glucose solution, which makes them practically painless. Their bismuth content is, of course, high. The oil suspensions include sodium potassium bismuth tartrate, metallic bismuth, bismuth oxid, quinin iodobismuthate and bismuth salicylate. These preparations are less painful than the aqueous suspensions. The soluble bismuth compounds are regarded with disfavor by the author because of the painful reactions which they produce and their higher toxicity. Lomholt has shown that the oil suspensions are very slowly absorbed as compared with the aqueous suspensions and commends, therefore, bismuth hydroxid made up in 10 per cent glycerin. Barthelemy showed that bismuth oxids which are coarse and granular tend to produce abscess. The insoluble iodoquinate has a low bismuth content, but some of its favorable action is due to the tonic effect of the quinin. The most rapid spirillicidal action is obtained with the soluble tartrobismuthate, which is, however, too painful for general use. Between the soluble and the insoluble salts of bismuth one has a choice between pain and too rapid absorption in the soluble and relative painlessness with slow absorption and reduced therapeutic effect in the insoluble. The intravenous administration of colloidal bismuth is discountenanced on account of its high toxicity. Inunctions have been shown by Klauder to be inactive. The author strongly commends the deep subcutaneous in preference to the intramuscular administration of bismuth preparations. By this method bismuth hydroxid, the oxychlorid and metallic bismuth, all very effective salts, can be given without more than momentary discomfort. The injection must not be given near the skin but deep into the subcutaneous fat, which is done by pinching up the skin and subcutaneous tissues between the thumb and forefinger and injecting the solution onto the fascia covering the muscles beneath (hence essentially epifascial injection). A fatal case following injection of bismuth into the blood stream through a deep vein which had been accidentally entered is reported by Chenoy. Emphasis is placed on the fact that deep subcutaneous injection can be given at almost any spot on the buttock, and Harrison's practice of giving an injection of an arsenical preparation through the same needle as the bismuth and at the same site is noted.

Therapeutic Results. In discussing the therapeutic results of bismuth therapy, Davies states that many observers have been disappointed by its therapeutic action since the original reports. The wide divergence of experience in the literature is brought out, with competent observers asserting that in late syphilis and Wassermann-fast cases, for example, bismuth does, and with equal emphasis does not, cause the blood Wassermann to become negative. The author reports an investigation of two parallel series in which neoarsphenamin and mercury, and neoarsphenamin and bismuth were used in the treatment of early syphilis. In this series, aggregating 425 cases, it appeared that 81.7 per cent of completely negative Wassermann results was produced by mercury, as against 77.3 per cent in the bismuth series. The incompletely negative Wassermann reactions, indicating that a continuation of treatment was essential, were 6.7 per cent in the mercury series as against 14.1 per cent in the bismuth series. Average time of disappearance of spirochetes from lesions following treatment

with bismuth salts is five or six days. One gram of metallic bismuth is usually sufficient to cause the disappearance of secondary lesions (Chenoy). Denny noted that cutaneous secondary recurrences followed soon after an initial course of bismuth treatment. Herxheimer reactions occur in 20 per cent of patients treated with bismuth. Gummatous ulcerations and tibial periostitis which relapse or refuse to heal under arsenic or mercury respond favorably to bismuth. Arsenic jaundice tolerates the drug well. A number of observers have noted that the mouth lesions of syphilis are especially favorably influenced by bismuth.

In the treatment of neurosyphilis bismuth appears to be more valuable than mercury in the amelioration of tabetic symptoms. Lightning pains, gastric crises and urinary incontinence are notably affected. The results in general paresis are *nil*. A number of observers seem to agree that the influence of bismuth on the subjective symptoms of neurosyphilis is better than that of the majority of other drugs. Musser has especially commended its action in cardiovascular syphilis and nephritis in preference to arsphenamin. Bismuth is the drug of choice in the treatment of coincident pulmonary tuberculosis and syphilis. It appears that there are cases in which bismuth is a conspicuous failure and a number of examples of relapse and recurrence have been reported. The French observers are inclined to consider that the curative value of the drugs now used in the treatment of syphilis stands in this order: Arsenobenzol, 10; bismuth, 7; mercury, 4. The author disagrees and considers mercury more nearly the equal of bismuth. The symptoms of intolerance to bismuth are less marked and more rapidly recovered from than those of mercury. Loss of appetite, vague indigestion, loss of weight, sleeplessness, depression, slight albuminuria and a blue line on the gums are the early signs. The blue line, however, may be absent in severe bismuth poisoning. Bismuth dermatitis and intractable Vincent's angina have both been noted in conjunction with bismuth administration and bismuth appears to predispose directly to the latter infection. Albuminuria associated with bismuth disappears more rapidly than that of mercury. The authors' summary of the place of bismuth in the treatment of syphilis emphasizes the fact that nothing but disappointment and retrogression in the general progress now being made against syphilis will follow any attempt to substitute it for arsphenamin. He cites the recent summaries of Jadassohn in Germany and Jeanselme in Paris, together with the experience of the treatment centers in England and Wales as demonstrative of this fact. It appears that there has been a 50 per cent decrease in the number of syphilitic cases seen in both England and France between 1919 and 1923. During the past four years, however, from 1923 to 1927, there has been a recrudescence of syphilis in France, where bismuth has had the most enthusiastic and general acceptance. This has amounted even to a rise of 20 per cent in the number of recently infected cases in Paris, though the migration of foreign workers is also considered a factor in this increase. The author considers that bismuth will replace mercury only to a certain extent. Its lower toxicity, the fact that it can be satisfactorily used during and after jaundice associated with the arsphenamins, and that it will apparently deal to some extent with cases resistant to mercury and arsenic are special indications. Alter-

nate courses of mercury and bismuth are commended by a number of observers. Giemsa has found that spirochetes transferred from one rabbit to another develop resistance to inadequate doses of sodium tribismuthyl tartrate, and Klauder has demonstrated the same thing to occur in subcurative doses of arsenobenzol.

The author's final paragraph deserves quotation: "I would like to sound a note of warning against the indiscriminate use of the bismuth compounds if the best therapeutic results are to be obtained. Sufficient time has not elapsed for us to decide whether bismuth or mercury is more effective, but the results after four years of bismuth therapy do not warrant the wholesale adoption of bismuth to the extinction of mercury. In spite of the fact that bismuth has been enthusiastically adopted, thoughtful workers will question the advisability of discarding mercury at this stage of our knowledge, for the ascendancy of bismuth over mercury in the cure of syphilis has not been established, although the easy convenience of the painless administration of an insoluble bismuth compound is an important factor in dealing with frail humanity. In general, the results of workers in this country have not confirmed the findings of Levaditi and his coworkers in France, and, although bismuth is convenient to administer, it seems doubtful if it will succeed in replacing mercury entirely in the chemotherapy of syphilis." A bibliography of sixty titles is appended.

OBSTETRICS

UNDER THE CHARGE OF

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Indications for Surgical Intervention in Pelvic Lesions of Infectious Origin.—CURTIS (*J. Am. Med. Ass.*, 1927, **89**, 1191) presents his work after many years of surgical work and study in the management of patients with pelvic inflammatory disease. He refers to his article of 1914 on the vaginal discharges, in which he gives Skene's ducts and the uterine cervix as the chief source of infection. The modern belief is that endocervicitis is the essential lesion in the chronic leucorrheas. Overenthusiastic cautery treatment of the cervix often leads one to the neglected Skene's ducts. He gives the bacterial flora of the examination of the vaginal discharge, laying particular stress on the diplococci which were found in 30 per cent of patients suffering with purulent discharge. He lays great stress on endocervicitis and its failure to heal spontaneously, giving insufficient drainage as his reason. Stric-

tures of the cervical canal frequently occur from overzealous cauterization. Endometritis is carefully reviewed and acute endometritis following a diagnostic curettage shows the importance of bacterial invasion of the uterine cavity. The inflammatory lesions of the adnexa are discussed. The methods and kinds of infections are presented. Clinical conservatism and discontinuance of operation have lead to the pelvic operation now being directed to the reconstruction of these tissues laid waste by disease, in preference to the removal of pelvic organs by operation to stamp out the disease. The author is led to believe that the kind of infection present in pelvic inflammation is to be somewhat of a guide during operation. As to whether the ovary shall be sacrificed or conservatism practised, his present attitude is toward conservation of healthy ovaries in young women who are subjected to total hysterectomy. He favors the discontinuance of salpingitis operations in acutely diseased tubes, as the author is against operation where acute infections are concerned. Absolute clinical conservatism combined with laboratory study has brought about the belief that gonorrheal infection of the Fallopian tubes and adjacent tissues is ordinarily a self-limited infection and that the so-called chronic cases are typically reinfections rather than a continuance of the process. Large pus tubes which persist and repeated attacks of salpingitis are almost pathognomonic evidence of reinfection. Surgery should be reserved chiefly for the sequelæ of infection, as the greater length of time given the preoperative convalescence the greater chance will be that the operative procedure may be constructive and conservative rather than radical and destructive. He concludes that chronic leucorrhea treatment should be directed to the uterine cervix as well as Skene's ducts; that thorough drainage is the greatest factor in the cure of chronic endocervicitis; that it is difficult to invade the uterine cavity without introducing bacteria; that operative intervention should be avoided where acute inflammation of the tubes exists; and that a decision at the time of operation, as to the disposition of a doubtful ovary requires most careful consideration of the etiology in pelvic infection.

Spinal Anesthesia in Obstetrics.—COSGRAVE (*Am. J. Obst. and Gynec.* 1927, **14**, 751) has used this method in 54 cases, which included practically all obstetric procedures. The only contraindication is hypotension. It is not used for first-stage analgesia by reason of its short duration. Its most frequent use should be in cases of toxemia where operative interference is indicated.

An Analysis of Maternal and Fetal Deaths in a Series of Two Hundred and Ninety-one Cesarean Sections.—MILLER (*Am. J. Obst. and Gynec.*, 1927, **14**, 773) states that during the years 1921 to 1926 inclusive 291 Cesarean sections were performed in six New Orleans hospitals. The incidence was 1.93 per cent. The operation was elective in 18.2 per cent and a definite test of labor was allowed in 8.2 per cent. The principal indications were contracted pelves, eclampsia, other toxemias, placenta previa, premature separation, previous abdominal deliveries and undilatable cervices. Recovery was febrile in 63.5 per cent. Dilatation of the stomach was a marked feature in 17 cases. The

maternal mortality was 16.1 per cent; fetal mortality, 18.9 per cent. The author calls attention to the large number of eclamptics who were in the group (41), 17 of whom died, and shows the inadvisability of this procedure on these cases. He points out that their mortality in the elective cases is high (5.5 per cent), also that in the last two and a half years 31 operations were done by the low cervical technique without a fatality.

The Toxemias of Pregnancy in Relation to Chronic Cardiovascular and Renal Disease.—CORMIN and HERRICK (*Am. J. Obst. and Gynec.*, 1927, **14**, 783) studied 291 cases at the Sloane Maternity Hospital. They were classified as: (1) Acute convulsive toxemias; (2) nephritic toxemias; (3) hypertensive toxemias. They observed that cardiac hypertrophy, thickening of the radial arteries and certain eyeground changes were present in a large proportion of these cases during the toxemias and during the follow-up period. This suggests that some disorder antedated the pregnancy; the types are, therefore, not mere complications of pregnancy. It probably reveals rather than causes the disease.

Cortical Necrosis of the Kidney in Pregnancy.—MANLEY and KLEMAN (*Am. J. Obst. and Gynec.*, 1927, **14**, 802) report a case of a primipara, eight months' pregnant, who was in good health until sudden onset of symptoms of concealed hemorrhage. The patient was delivered by Cesarean section. She had almost a complete anuria for twelve days before death, excreting only 831 cc. of urine. The creaturin rose to 12.5 mg. the last four days. Autopsy showed extensive cortical necrosis with purulent pyelonephritis most likely due to toxic products formed from the dead fetus.

Backache from an Obstetric and Gynecologic Standpoint.—ADAMS (*Am. J. Obst. and Gynec.*, 1927, **14**, 742) studied 943 consecutive patients. Of these 243, or 24.3 per cent, complained of backache alone or in conjunction with other symptoms. He concludes that abnormal pelvic conditions may cause this symptom, but the correction of their pelvic pathology does not give relief. Correction of faulty postures leads to a good prognosis. In this series posture was the underlying cause in 37 per cent. The next most frequent was retroversion, 15 per cent. Poor posture is often the result of overstretching of the abdominal walls during pregnancy. This should be prevented by proper support and reconstructive exercises.

Hemorrhage in Pregnancy.—MCCLUSEN (*Canadian Med. Assn. J.*, 1927, **17**, 2185) discusses abortion, accidental hemorrhage and placenta previa. He thinks accidental hemorrhage should be treated conservatively unless of the severe type, which should have section. Placenta previa, he believes, is being treated more and more by section and justifiably so. In the Winnipeg General Hospital in 2000 deliveries accidental hemorrhage occurred 9 times and they were all moderate cases. In the same series placenta previa occurred 16 times. In the 9 cases that version was done not a child survived. There was only 1 maternal death.

GYNECOLOGY

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Treatment of Pelvic Inflammatory Disease.—The treatment of pelvic inflammatory disease is far from standardized although perhaps many of the gynecologists in this country will take the attitude that the last word has been said upon this subject. In Great Britain, for several years there has been a continuous controversy concerning the proper manner of handling this condition and at the Sixth British Congress of Obstetrics and Gynecology, which was held in Manchester in April 1927, the subject was thoroughly discussed in a splendid symposium, the high spots of which I shall attempt to present. In discussing the treatment of acute gonorrheal salpingitis, BOURNE (*J. Obst. and Gynec. of the British Empire*, 1927, **34**, 185) still advocated early operation for the severe cases in which suppuration was present. He believes that the operation of choice is a salpingostomy but great care should be taken not to leave a tube which can obviously never perform its function. During convalescence he treats the uterus with frequent injections of glycerin and protargol and after convalescence final assurance should be made that the cervix and urethra are free from gonococci. In recommending the expectant treatment of pelvic inflammation, WHITEHOUSE (*J. Obst. and Gynec. of the British Empire*, 1927, **34**, 190), of London, stated that the initial mortality will be low. There is a strong probability that surgical treatment will be required at a later date but it will be undertaken at a time when such intervention is safe and with a correspondingly low mortality. It is only in a comparatively small proportion of cases that radical measures such as hysterectomy will be necessary after such conservative surgical treatment. The results of combined conservative and expectant measures are good, if by that is understood the production of an individual who is subsequently able to carry out her functions, social and marital, in a normal manner and with comfort to herself. On the other hand, fertility is impaired although not by any means destroyed. In the event of very acute infections and always in the presence of suppuration he believes that drainage should be instituted. The advent of pus removes the case from the "expectant" category and in this respect his views are in accord with those of Bourne. Even if and when the infecting virus dies the retention of pus tubes cannot but be a menace to the life and health of the individual. If drainage is instituted it should be by the vaginal route wherever possible. Our own CURTIS (*J. Obst. and Gynec. of the British Empire*, 1927, **34**, 199), of Chicago, stated that gonorrheal invasion of the Fallopian tubes and adjacent tissues tends to produce a self-limited infection, while the disease in

so-called "chronic" cases is typically a reinfection. He is of the opinion that operative interference should be avoided in patients with acute inflammation of the tubes, complications seldom necessitating deviation from this rule. Surgery should not be employed routinely for the purpose of eradicating tubal infection but should be reserved chiefly for the sequelæ resultant from bacterial invasion. Adhesions of gonococcal origin are almost invariably amenable to smooth separation by blunt dissection with scissors, and large omental transplants afford a suitable covering for extensive raw surfaces in the pelvis which would otherwise remain denuded. He believes that a healed hydrosalpinx of moderate size sometimes causes least trouble if left undisturbed, while plastic operations upon definitely thickened tubes have never relieved sterility in his patients. Less seriously diseased tubes may be rendered patent by gentle dissection with scissors of the invaginated fimbriæ, and apparently healthy tubes may be relieved of occlusion by means of air inflation from within the abdomen. Preservation of the ovaries appears desirable unless they are badly crippled or the circulation is impaired. If one ovary must be sacrificed he believes it is inadvisable to resect the remaining one as the remaining fragment only keeps alive a spark of sexual vigor and the patients suffer for years with the symptoms of a partial menopause. In the presence of a diseased ovary, with the indications for removal somewhat uncertain, less radical surgery appears indicated in gonorrheal disease than in streptococcal or tuberculous infection of equal severity. Those who advocate early operation emphasize the shorter period of incapacitation enjoyed by patients subjected to surgical intervention. However, his experience of recent years indicates that we have been in error in accepting this belief. Convalescence under palliative care is quite as prompt and yields even more satisfactory results in the great majority of cases in which it is the treatment of choice. He is certain that even those who have been repeatedly infected tend to ultimate recovery if isolated from consorts who are carriers of disease. The operative treatment of chronic salpingo-oöphoritis was presented by CAMERON (*J. Obst. and Gynec. of the British Empire*, 1927, **34**, 206), of Glasgow, who stated that in severe cases associated with dense adhesions, he formerly practised the operation of bisection of the uterus followed by transverse division of the cervix but on account of the possibility of contamination of the peritoneum he has abandoned it in favor of two other methods. In the one method, he performs complete hysterectomy with Wertheim clamps instead of opening the vagina as is commonly done, and after removal of the uterus, the stump is treated with carbolic acid. The other method which he uses when the right-angled clamps of Wertheim are not available is a combination of vaginal and abdominal hysterectomy, the uterus being removed by the vagina so that there is very little chance of infecting the peritoneal cavity. In dealing with young women he prefers the Blair Bell operation but in addition the cervix should receive special treatment if discharge be a prominent feature in the case, and this should be done before the abdomen is opened to avoid placing a strain on the ligatures on the large vessels. Ovarian conservation in these cases is the subject which was presented by BLAIR BELL (*J. Obst. and Gynec. of the British Empire*, 1927, **34**, 213), of Liverpool, who is one of the best known British gynecologists.

He stated that there are those who always remove the ovaries when operating for salpingitis and those who will go to any trouble to conserve this organ and its function. To him, ovarian conservation is a surgical axiom and he considers the indiscriminate "clean-sweep" removal of ovaries as a routine procedure a surgical sacrilege. It is all very well to say that the patient still has her thyroid, suprarenals and so on, and that the ovary is only part of her sexual make-up; in fact, he was responsible many years ago for the aphorism *"Propter secretiones internas totas mulier est quod est;"* but would anyone disregard the preservation of a beautiful nose because the woman had a beautiful mouth? It is the *tout ensemble* that counts. In brief, the substance of his paper was that the ovaries should be preserved whenever possible and when they could not be preserved in their normal position on account of interference with the blood supply, autoplastic ovarian grafting should be performed in women under forty years of age. In his experience, ovarian grafting in cases in which the uterus was not totally removed preserved menstruation in 72.1 per cent of the cases, while menopausal symptoms were averted in 88.7 per cent of all cases. The end results of salpingostomy in chronic salpingitis with special regard to pregnancy was the subject presented by SOLOMONS (*J. Obst. and Gynec. of the British Empire*, 1927, **34**, 218), of Dublin. He stated that in every case of sterility in which the man is not at fault and when there is no contraindication to its use, the Fallopian tubes should be tested. If the tubes are not patent, the abdomen should be opened. The prognosis for cure by salpingostomy is better when the block is at the fimbriated end of the tube than anywhere else. While the results are not startlingly favorable at present, he believes that we are justified in performing salpingostomy followed by the insertion of a piece of catgut in the tubal lumen in order to keep the tube patulous. He described in detail his procedure of bisecting the uterus in the performance of the operation which he stated is a definite advance in the technique. The symposium was followed by a very long and animated discussion in which the speakers expressed anything by unanimity of opinion. As I said in the beginning, the gynecologists who believe that the last word has been said upon this subject have a rude awakening in store for them although I truly believe that in this country the treatment of pelvic inflammatory disease is more nearly standardized than it apparently is in Great Britain. My own feeling in the matter is that if we follow the teachings of Blair Bell in regard to ovarian conservation and of Curtis in regard to operative conservatism, we shall have a lower mortality and fewer postoperative wrecks. I am becoming more and more conservative as time goes on in the matter of operating upon cases of chronic pelvic inflammatory disease and I now send many patients out of the hospital without operation after the subsidence of their acute exacerbations upon whom formerly I would have operated. For the most part they remain free from symptoms if they avoid reinfection and even if they should later require operation on account of some distressing sequel, they will be in much better shape to withstand it in from three to six months later than within the customary one or two weeks after the subsidence of the fever. The subject is still a live one for discussion but in the present state of our knowledge I would unhesitatingly cast my lot with the conservatives.

OPHTHALMOLOGY

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Spasmodic Associated Movements of the Eyes: Can They be Produced by Syphilis.—Spasmodic associated movements of the eyes have recently been observed by PEARSON (*Arch. Neurol. and Psychiat.*, 1927, **18**, 414) in a number of cases of encephalitis of the Parkinsonian type. As these cases have been reported only clinically and no pathologic study has been made, the location of the lesion as well as its character is not clear. Various authors have placed the lesion in the corpora striata, the corpora quadrigemina, the pallidum. Some attribute the attacks to inflammation in the midbrain and others to a lesion in the supranuclear tract, as the spasms resemble supranuclear epilepsy. Most of the authors conclude that it is in the corpora striata. "It does not seem reasonable," to the author, "to believe that irritation of the corticonuclear pathology could continue over an extended period of time, such as has elapsed in these cases, without resulting eventually in the interruption of the tract and cessation of function. Furthermore, if the symptoms were produced by irritation one would expect it to appear early in the course of the disease, and in none of the reported and personally observed cases has it appeared earlier than one year after the development of the associated Parkinsonian condition. A similar line of reasoning tends to refute the theory that irritation, either of the lower midbrain centers or of the corpora striata, is the causative factor, for, though it is well known that active lesions of encephalitis are present even years after the inception of the disease, it would seem strange that these irritative lesions would not produce the symptoms earlier in the life history of the condition." A case report is given of a colored woman, aged twenty years, who had spasmodic movements of the eyes in which the eyes were drawn strongly upward and she was unable to move them in any direction while the spasm lasted. The attack occurred about every two or three days and usually lasted ten minutes. Two years before she had developed signs of encephalitis. The blood was strongly positive to the Wassermann test and the cerebrospinal fluid was under pressure of 14 mm. Hg, there were three cells, a faint trace of globulin and the Wassermann reaction was negative. The author did not believe that in this case a diagnosis of syphilitic disease of the corpora striata could be made. All the evidence points to the etiologic factor being encephalitis of the epidemic type.

Protein Therapy—Specific and Nonspecific in Ophthalmology.—WOODS (*Ohio State Med. J.*, 1927, **23**, 740) reports that there are four phases in the use of specific therapy in ophthalmology about which there is still a great diversity of opinion: (1) Tuberculin therapy is employed with good effect by some clinicians and is condemned by

others. At the Wilmer Institute of the Johns Hopkins Hospital the object in the diagnostic use of tuberculin is to determine whether or not an unusual degree of tuberculin hypersensitivity exists, and at the same time to avoid a focal reaction in the eye. Intradermal injections in the forearm are made with 0.05 cc. of different dilutions of tuberculin: 1 to 1,000,000, 1 to 100,000, 1 to 10,000 and 1 to 1000. The smaller doses are first given, the larger doses only when the reactions to smaller doses are negative. He emphasizes the following points in the use of tuberculin: (*a*) Great care should be exercised in the diagnostic use of tuberculin to avoid focal reactions; (*b*) the initial dose of tuberculin should always be very small and graduated in relation to the degree of hypersensitivity; (*c*) tuberculin therapy should be instituted only after all manifest foci of infection have been eradicated, and should not be started until the patient has recovered from the effect of the eradication of such foci of infection; (*d*) after treatment has been finished the patient should be watched for a return of the hypersensitivity. (2) Vaccine therapy has been found to be of value in the treatment of blepharitis, dacryocystitis, conjunctivitis and such conditions, by the application and instillation of the antivirus specific for the bacterium causing the morbid ocular condition. (3) Uveal pigment therapy appears to be of very definite value in the treatment of sympathetic ophthalmia. (4) Lens protein therapy, advocated in this country by Davis and others for the prevention and absorption of cataract, has not been used by the author "nor does it seem wise to hazard any opinion in a subject where there now exists so little evidence for its rationale." Lens protein may be used to desensitize an individual on whom a cataract operation is to be performed.

Notes on Two Cases of Renal Retinitis.—Terrien (*Franco-British Med. Rev.*, 1927, **3**, 315) states that renal retinitis is characterized clinically by four principal lesions, viz: Symptoms of neuritis in the papilla; edema of the papilla so pronounced it may simulate papillitis; white patches more or less disseminated around the papilla and situated, as a rule, behind the vessels; hemorrhagic points in the internal layers. As a general rule, the diagnosis of nephritic retinitis can be made merely by examining the fundus, but when the lesions are isolated it may become a more delicate matter. The first symptom is usually diminution of vision which is marked in proportion to the extent of the mischief, though it may be pronounced even in the presence of apparently slight lesions, and in such cases it may be due to diminution of sensitiveness on the part of the retina resulting from toxic influences. It does not seem that vascular lesions have much to do with the production of albuminuric retinitis, which in all probability is consequent upon toxic influences. The author is convinced that this type of retinitis is found almost exclusively in subjects who present an excess of urea in the blood (azotemia). Nevertheless we are not justified in assuming that azotemia is a *sine qua non* of retinitis because it is sometimes found in persons who are not suffering from uremia and whose blood is normal. It follows that there must be some other cause than a mere excess of urea; in fact, poisons that are not being eliminated by the kidneys and infiltrate the tissues. The prognosis is always grave. There is no indication for local treatment.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Endocrine Hypofunction in Ear Disease.—While of relatively recent date, the intensive study of the glands of internal secretion has caused a reconstruction of some of the most fundamental concepts of general biology. In incipient hypofunctional states, which are of common occurrence in general practice, the changes are tendential rather than established so that careful analysis is necessary to make even the most tentative of diagnoses. On the other hand, the primary elimination of potential nonendocrine morbidity is of basic importance. Where there is functional derangement due to glandular deficiency, the symptomatology in adults is one of general debility and lowered vitality. The lowered metabolism affects the vegetative functions, possibly causing irritability and depression, pruritus, paresthesia, reflex gastric and intestinal disturbances, vague malaise and indefinite muscle and joint pains. Inasmuch as deficiency of any given hormone may produce manifestations far removed from the immediate focus of failure, and, as dysfunctional types may integrate diverse activities of the several functional components of a complexly functioning gland, DRURY (*J. Laryngol. and Otol.*, 1927, **42**, 375) discusses the otological manifestations, which he has encountered in these conditions. Clinical records are produced to illustrate the four groups into which he has divided the cases from a symptomatologic point of view. These groups of symptoms included tinnitus, vertigo and fatigue; recurrent coryza, headache and definite neuralgia; intermittent deafness, arthritis, psychic changes and neurasthenia; and eczema of the auditory canals, intermittent deafness and vasomotor disturbances. In all instances the basal rate was low, varying from −20 to −24; the temperature was subnormal in all save one; the pulse was usually slower than normal, and there was, as a rule, hypotension. In discussing the problem, the author calls attention to the great diversity of symptoms, seemingly unrelated and not explainable except on an endocrinologic basis, which are encountered in dysfunction of the thyroid gland. The characteristic mentality of the aged, with loss of memory, tendency to somnolence and lack of grasp of difficult or complex matters has its counterpart in that of marked dysfunction. The impaired hearing, tinnitus, vertigo, dry and scanty hair and arteriosclerosis of the one are likewise characteristic of the other. Often there is a swelling of the mucous membranes, causing a nasal obstruction which is not relieved by operation. The impairment of hearing has been attributed to the swelling of the Eustachian tubal and tympanic mucosa, and tinnitus to the infiltration of the auditory nerve, as well as to a loss of vascular tone and imperfect circulation. The author advises thyroid medication in these cases, rather than surgery, although he emphasizes that thyroid

medication is indicated only in those cases where thyroid failure has been demonstrated. He admonishes that it is a specific replacement therapy—not a panacea—mentioning also that improvement can be expected in supplying anterior-lobe extract in certain groups of pituitary deficiencies. In all these conditions, however, the treatment must be administered continuously in order to prevent reappearance of symptoms.

Laryngeal Complications of Irradiation.—"Any agent that has the power to do good when rightly used has the power to do harm when wrongly used." Applying this aphorism to the use of the Roentgen ray and radium as therapeutic agents in laryngeal disease, CLERF (*Arch. Otolaryngol.*, 1927, **6**, 338) condemns the use of radium in recurring papillomata of the larynx in children, citing 4 cases which exhibited such untoward effects as perichondritis, loss of cartilage, extensive fibrosis, cicatricial stenosis, even to complete closure of the laryngeal lumen. Seldom does the radium exert an inhibitive influence or curative effect, and in some instances seems to activate the rapidity of repullulations. Repeated superficial removals with blunt, noncutting forceps will ultimately give excellent results as far as voice and freedom from recurrence are concerned. Two case reports are presented to illustrate the destructive effect on the larynx and cervical tissues following Roentgen ray treatment of the thyroid gland for exophthalmic goiter. The author further states that indiscriminate treatment of laryngeal cancer by irradiation should be discouraged, and that patients with operable cases of cancer should not be treated except on the advice of the surgeon and radiologist. He believes that tissue sensitivity, individual susceptibility, cumulative effect and filtration are problems for the experienced radiologist.

RADIOLOGY

UNDER THE CHARGE OF

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Roentgen Diagnosis of Aortic Disease.—NICHOLS (*Radiology*, 1927, **9**, 136) points out that although aortic disease is relatively common, many cases remain undiagnosed until a late stage is reached. Early clinical symptoms which should lead one to suspect the presence of aortitis are (1) shortness of breath on exertion and a feeling of oppression in the chest; (2) sighing respiration; (3) a feeling of oppression in a close room; (4) pain of anginal character; (5) orthopneic dyspnea. In the majority of cases aortitis is of syphilitic origin and a positive Wasser-

mann reaction or a history of luetic infection is important in the diagnosis. For early diagnosis, confirmation of the clinical diagnosis and determination of the extent of disease the Roentgen examination is most reliable. Fluoroscopy is not sufficient and films should be made in the sagittal, transverse and oblique positions. Dilatation of any degree or aneurysm of the aorta will be apparent in the roentgenogram. In addition the aortic shadow is increased in density and this is an important indication. Pulsation is usually increased in the early stages of aneurysm but later may be diminished as a result of the pathologic changes.

Tubal Pregnancy; Radiography after Injection of Lipiodol.—VIALLET and JAHIER (*J. de radiol. et d'electrol.*, 1927, **11**, 416) report this case in a woman, aged fifty-five years. Lipiodol was injected into the uterine cavity under fluoroscopic observation. The uterine cavity and right tube were filled completely, but the left tube was obliterated about 5 cm. from its origin. Details of the fetal skeleton were not complete, but the cranium, thorax and some of the long bones were revealed. By correlation of the clinical and roentgenologic data a diagnosis was made of left tubal pregnancy with death of the fetus at term, three months prior to examination. The diagnosis was fully confirmed at operation. In a case previously reported by Zimmern, one of extrauterine pregnancy at term, the lipiodol was not retained and neither the uterine cavity nor tubes were depicted.

Endothelial Myeloma.—SYCAMORE and HOLMES (*Am. J. Roentgenol. and Rad. Therap.*, 1927, **18**, 223) observe that, although endothelial myeloma, or Ewing's tumor, is generally considered to be rare, it is probable that the condition is of more frequent occurrence than is commonly supposed, its presumed rarity being due to failure of diagnosis. While estimates of its incidence vary, it probably constitutes 10 per cent of all bone tumors. The roentgenogram is the most important single piece of evidence in the diagnosis, since the picture is usually characteristic. Endothelial myeloma is seen as a purely destructive nonosteogenic process in the bone. There is a widespread, even, diffuse absorption of bone, usually involving over one-half of the shaft. The process begins characteristically near the center of the shaft and extends toward both ends. It quickly invades the cortex and periosteum, and there may be a periosteal reaction which simulates that of infectious periostitis. New bone laid down as a result of this proliferative reaction is usually in layers parallel with the shaft, but occasionally there is a tendency to form radiating spicules similar to those seen in osteogenic sarcoma. When the tumor growth actually invades ing over one-half of the shaft. The process begins characteristically near the center of the shaft and extends toward both ends. It quickly invades the cortex and periosteum, and there may be a periosteal reaction which simulates that of infectious periostitis. New bone laid down as a result of this proliferative reaction is usually in layers parallel with the shaft, but occasionally there is a tendency to form radiating spicules similar to those seen in osteogenic sarcoma. When the tumor growth actually invades the periosteum it destroys rather than elevates,

in contradistinction to subperiosteal sarcoma or to subperiosteal abscess formation. The tumor slowly invades the soft parts, often being fairly well outlined. A striking feature of the Roentgen picture is the even, diffuse absorption of a large segment of the shaft of the bone. The shaft does not retain its density as is usual in osteogenic sarcoma. Destruction is more even and excites less proliferative reaction than is produced by chronic inflammation. Metastatic hypernephroma may simulate Ewing's tumor very closely. Irradiation is the treatment of choice and the response is often so marked as to be startling, and, although the prognosis is poor, the patient may be kept apparently free from disease for several years. The place of surgery is a disputed question, and the value of Coley's serum is doubtful.

Roentgenologic Aspects of Primary Tumors of the Lung.—HYDE and HOLMES (*Am. J. Roentgenol. and Rad. Therap.*, 1927, **18**, 235) report in tabular form the findings in 13 cases of primary cancer of the lung, chiefly bronchial, and 1 of teratoma. The writers hold the opinion that primary tumors of the lung are not as rare as is commonly believed. A correlation of the clinical and roentgenologic findings is necessary for the diagnosis. Rarely the Roentgen findings present features which are practically pathognomonic. Among the more suggestive findings is that of a dense hilar mass with nodules and radiations extending into the lung field. The most common typical tumor is a carcinoma of the right bronchial tree of a male in the fifties, appearing as a hilar shadow with radiations extending into a small immobile lung field, but it may be obscured by shadows of complicating conditions.

Importance of Roentgenography in Mammary Cancer.—BENDIC (*Am. J. Roentgenol. and Rad. Therap.*, 1927, **18**, 244) stresses the fact that before submission to operation for mammary cancer the patient should first have a roentgenographic examination of the chest and pelvis for possible metastasis to the lungs or bones. While both should be examined, the pelvic examination is especially important, for, contrary to former belief, metastasis to the bones is more common than metastasis to the lungs. The most frequent sites of metastasis are the lumbar vertebræ, one or both sacroiliac synchondroses extending out into the ilium, the descending ramus of the pubic bones and in the region of the trochanters. The skull and long bones come next in frequency. Any bone may be involved, but metastasis below the knee and elbow is rare. Metastatic lesions in bone from mammary cancer are characterized by a combination of destruction with proliferation, one or the other often predominating markedly. In the productive type distinction from Paget's disease may be difficult, but a roentgenogram of the head will decide the question as Paget's disease of the skull is typical.

A New Iodin Compound for Cholecystography.—KIRKLIN and KENDALL (*Radiology*, 1927, **9**, 205) have produced and tested the di-iodo-diethyl-ether of di-salicylphthalein. It is a white, crystalline powder and a 10 per cent aqueous solution of its sodium salt, the form in which it has been given to patients by mouth, is clear, colorless, odorless, and slightly bitter-sweet in taste, with a transitory warmth as of peppermint which is not objectionable. After experiments on dogs, the drug was

given orally (7.5 to 10 gm. in 100 cc. of water) to 35 patients. None of the patients vomited though several had vomited after taking sodium tetrabromphenolphthalein, and the shadows were better than those obtained from the bromine salt. Two patients were purged unpleasantly, but one of these had recently had diarrhea. No patient had any other ill effects. The drug has not yet been produced in quantity.

Cholecystography.—SHERWOOD MOORE (*Radiology*, 1927, **9**, 200) who has been associated with Graham, Cole and Copher in the development of the method says that of 147 cases submitted to cholecystography and later to operation 143 have indicated a correct preoperative opinion. Sodium phenoltetraiodophthalein is the substance of choice and it is given intravenously. His early material contained some few cases in which cholecystography would not be omitted, but after a little experience the procedure was carried out only on patients in whom the diagnosis was not at all clear from clinical and laboratory data. Moore feels that it is in the case with obscure symptoms that cholecystography finds its most important use.

Oral Cholecystography.—As there is no standardized technique MENEES and HOLLY (*Radiology*, 1927, **9**, 213) have attempted to determine the relative value of three methods. Sodium tetraiodophenolphthalein was given in Whitaker's stearic-acid coated pills to 100 patients; in formaldehyde-hardened capsules to 100; and in Oakman's salol-coated capsules to 100. The Oakman method gave the largest percentage of satisfactory shadows.

Roentgen Irradiation in Rheumatic Endocarditis.—With the idea of attempting to influence rheumatic lesions in the myocardium, 20 patients with rheumatic carditis were given 139 irradiations to the heart by LEVY and GOLDEN (*Am. J. Roent. and Rad. Ther.*, 1927, **18**, 103). The machine setting was calculated to yield $\frac{1}{16}$ of the erythema dose distributed throughout the heart muscle. Frequent electrocardiograms and numerous teleroentgenograms were made. Changes in the form of the electrocardiogram were observed in 14 of the 20 cases. The changes were similar to those sometimes found in the course of rheumatic fever and regarded as due to myocardial involvement. It is suggested that the alterations noted following roentgen irradiation of the heart occurred as a result of the action of the rays on the tissues of the heart with modification of the rheumatic lesions. No changes were observed in the teleroentgenograms which could be ascribed to roentgen irradiation. Of the 20 cases, 17 showed definite improvement. The value of roentgen irradiation of the heart as a therapeutic measure in rheumatic carditis is not stressed on the basis of these observations, because of the small number of cases studied and the relatively short period of follow-up. A detailed clinical study will be reported at another time. In 8 patients, mildly unpleasant symptoms were noted. In no instance was there evidence of cardiac injury or unfavorable effect on the course of the disease. In 2 cases of Streptococcus viridens endocarditis, roentgen irradiation of the heart caused no change in the form of the electrocardiogram nor did it modify the fatal progress of the disease.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Pathogenesis of Cerebral Hemorrhage—A Case of Aneurysm of the Posterior Communicating Artery.—HASSIN (*Arch. Neurol. and Psychiat.*, 1927, **17**, 770) presents a well studied case of aneurysm of the posterior communicating artery. Attempt is made to derive the physiopathologic mechanism of cerebral hemorrhage. Death in this case occurred due to rupture of this aneurysm which was associated with high blood pressure. The basal ganglia on the same side showed numerous extravasations of blood and in this area vascular changes were found, not aneurysmal in nature, but involving the intima and media of the smaller bloodvessels. There were occasional globular or ampular dilatations with rupture of the vessel walls, but most of the hemorrhages were extramural. Attention is called to the fact that these hemorrhages occur in another branch of the middle cerebral artery. Since no reactive phenomena were present it was concluded they were agonal in character. On this basis, the author rejects the older theories of the mechanism of cerebral hemorrhage but agrees with the general concept that two factors are necessary—changes in the vessel, the anatomic factor—and increased blood pressure, the physiologic factor. He believes that rupture of the large aneurysm at the base caused a fall in blood pressure in the middle cerebral artery and this caused a rise in pressure in the corresponding vein so that the already diseased walls of the striate vessels were further damaged and hemorrhage occurred. These were agonal in character. Miliary aneurysms are considered not essential in the genesis of cerebral hemorrhage. While most of the conclusions seem valid, one wonders why the venous pressure should increase locally with a fall in the local arterial pressure.

Mechanism of Compression in a Case of Tumor of the Cerebello-pontile Angle.—SCHALLER (*Arch. Neurol. and Psychiat.*, 1927, **17**, 609) reports a case of cerebello-pontile angle tumor studied by serial sections of the brain. The upper cervical cord showed no myelin degeneration. The medulla showed no abnormalities either internally or externally at the level of the pyramidal decussation. Flechsig's and Gower's tracts showed no degeneration. The restiform body was smaller on the side of the tumor at the level of the inferior olive and there was marked decrease in the fibers of the descending vestibular root. Dieter's nucleus and the triangular nucleus did not seem compressed. In

general, the brain stem was only slightly compressed, the right cerebellar hemisphere and middle peduncle bearing the greater damage. The dentate nucleus on the tumor side was poorer in fibers but not in cells; the eighth nerve was completely obliterated on this side, whereas on the opposite side its course was well marked. The cochlear nerve and nuclei were completely destroyed, facial nerve not affected and superior peduncles equal. The lower tegmentum showed compression of the aqueduct, suggesting danger of block. Above the red nucleus there were no abnormalities. From the above data they conclude that the incoördination in this case was due to injury to the middle peduncle, restiform body and the descending vestibular root and not to the direct compression of the cerebellum.

L'Epilepsie dans l'Encephalite Epidemique Chronique.—MIMMER (*Rev. de neurol.*, 1927, **2**, 269) states his experience leads him to look upon the rarity of persistent epilepsy in epidemic encephalitis reported in the literature as quite strange in that he has seen a considerable number of such cases. He divides his cases into two groups. The larger group comprises those cases in which the epileptic accidents are found associated with other more or less pathognomonic symptoms of encephalitis. The second group comprises a smaller number of patients in which practically monosymptomatic encephalitic epilepsy was observed. In this group it was necessary for diagnosis to use slight neurologic symptoms, minor vegetative disturbances, myoclonies and in some a history, more or less clear of an initial, typical state. In this article the author restricts himself to presenting his recent cases of monosymptomatic encephalitic epilepsy. Seven such cases are reported. He states that such epilepsy may follow directly after the initial illness, as in his second case, or after a more or less prolonged interval, more or less free from signs of illness. In his seventh case about eight years elapsed. He believes that in such cases the initial illness may be easily forgotten by the patient and if the case was cryptogenic in type, the doctor might easily fail to recognize the possibility that the epilepsy originated in encephalitis. As to the pathophysiologic mechanism, he states that it is necessary in the first place to consider the epilepsy as the expression of a continuously active inflammatory process in the brain and some cases demonstrate this well. In his opinion encephalitic epilepsy has for an anatomicopathologic foundation localized histopathologic alterations of the brain. In a good number of cases he found symptoms indicating lesions of the great basal ganglia, that is, hyperkinesis, choreiform or myocloniform tremors, vegetative disturbances, somnolence and so forth. In such cases the basal lesions are patent. This brings up the question of extrapyramidal epilepsy. The author states that in all such cases the convulsions present the tonic type in complete accordance with the doctrines of Binswanger and Ziehen. In the cases presented in this article the convulsions were of the tonico-clonic type. The author considers that if at the same time there are symptoms denoting lesions of the basal ganglia it would seem probable that there were also cortical lesions.

Ein Fall Von Symptomatischer "Narkolepsie mit Experimenteller Austosbarkeit der Anfälle."—ZADOR (*Monatsschr. f. Psychiat. u. Neurol.*, 1927, **66**, 13) presents a case of a patient, aged thirty-two years, who had had attacks for about four years. They began a few months after the removal of her left ovary with sudden onset. They recurred two or three times a day, but gradually diminished in frequency until they occurred every three to six months. Prior to admission she had been hit on the head during a quarrel and following this the attacks had recurred daily, at first several times a day. The character of the attack was as follows: The patient was able to note the approach of the attacks because she felt ill and dizzy. Her face appeared white, she felt sleepy and at first there was stiffness of the jaws. The eyes were open and drawn upward and the glance was staring. They then closed and she began snoring, breathing for one to two minutes. Breathing was then suspended for a half to one minute, after which it became deep but regular and without sound. There was no generalized convulsion, but in some attacks shaking of the left hand was noted. There was no tongue biting or loss of urine. The patient usually slept from five to ten minutes after which she would wake up knowing that she had been ill but having no memory for the attack itself, and was not able to relate any dreams. In the first one to two minutes of the attack there was a generalized hypotonus of the entire body which then passed away. After two or three minutes the patient could be awakened, but appeared sleepy, could not talk and looked strangely at the questioner. If left alone she would sleep for about ten minutes. The attacks were brought on experimentally by sound, smell and emotional stimuli, and these experimental attacks resembled the others in all respects. The history of the patient was interesting in that the mother had had an atypical form of epileptic attacks. The patient as a child had an unusually marked growth of hair on her face which she lost later. She had had many attacks of headache and dizziness, with occasional accompanying vomiting. From fifteen to eighteen years of age she had outspoken migraine which disappeared after the onset of her menses, but the menses were accompanied by illness and vomiting. Following the operation for removal of the ovary she developed a masculine type of facial hair distribution. The author distinguishes this from genuine narcolepsy by the following: (1) Epilepsy of the mother; (2) vasomotor attacks as well as migraine; (3) onset of the attacks coincident with endocrine disturbances and angiospastic attacks in the extremities; (4) experimental production of the attacks; (5) dizziness before the attack with occasional vomiting, unawakableness in the beginning, loss of tonus and unusual breathing. He considers that the epilepsy in the mother and the inability to awaken the patient in the beginning would indicate epilepsy, whereas the spontaneous remissions, the lack of response to luminol and bromids and the experimental production of the attacks would speak for a psychic origin. Because of its peculiarities, that is, its manifest similarity to narcolepsy and the indications of psychic origin, he classifies it as symptomatic narcolepsy. He compares narcolepsy and epilepsy from the standpoint of clinical picture and pathology and draws the conclusion that both are clinical syndromes. He advances the concept that narcolepsy is only a variant in the group of epilepsy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Studies on Endothelial Reactions: On the Origin of the Pulmonary "Dust Cell."—Foot (*Am. J. Path.*, 1927, **3**, 413) reports the results of further investigation of the origin of the pulmonary "dust cell." Two experiments were performed: In the first carmin was injected intravenously into a donor rabbit and after fifteen minutes 25 cc. of heart's blood were withdrawn, 8 cc. of which were injected intravenously into each of three rabbits, following which they received from 3 to 4 cc. of pasteurized milk containing 0.5 per cent of saturated alcoholic Sudan III. The rabbits were killed in twenty-four, forty-eight and ninety hours respectively. The second experiment duplicated the first except that different amounts of carmin were used, the heart blood was withdrawn in five minutes and 1 cc. of pasteurized milk diluted one-half with Ringer's solution was injected intratracheally. The cells that responded in the alveoli were examined *in vivo* in supravital films, the lungs were sectioned after freezing or embedding in paraffin and examined from the morphologic view. In addition to this, material from scraped human lungs and sputum from a patient with aortic insufficiency were examined in supravital films. Lung tissue was sectioned from similar cases and the findings later checked against fresh human spleen and a case of tuberculous meningitis. It was hoped by introducing marked monocytes to prove or disprove the blood origin of the intraälveolar phagocytes. By means of silver tannate impregnations it was found possible to specifically stain dust cells and distinguish them from other cells, particularly epithelial cells. From the results of the above work the author concludes that dust cells are probably forms of monocytes or blood histiocytes, and that while the tissue histiocytes may play some part in their formation their chief source is the circulating monocytes in the blood stream. The alveolar epithelium does not produce dust cells; it possesses totally different affinities for silver salts and can be readily differentiated by silver tannate impregnations. The assumption that there is no nucleated respiratory epithelium does not appear to be warranted.

Local and Systemic Changes Induced by Lipoid Solvents in Animals Fed on Diets Varying in Vitamin Content.—Joistead and Johnston (*Am. J. Path.*, 1927, **3**, 489) cite the results of further studies upon the local and systemic effects of lipoid solvents injected into animals fed on diets containing varying amounts of vitamin content. The experiments were performed for the most part on white rats and in

smaller numbers upon guinea pigs and monkeys. They consisted in the subcutaneous injection of coal-tar soot, produced by the action of ether upon coal tar, animal, vegetable and mineral oils, alone, and with chloroform, into animals fed on diets rich in vitamin A, deficient in vitamin A, balanced in vitamin content and also diets rich or deficient in carbohydrate content. They observed that the various oils and fats act like coal tar when injected into the subcutaneous tissue of animals. All dissolve the cell lipoids and may be classed as lipoid solvents. The cellular activity about droplets of various lipoid solvents is greatly increased by feeding diets rich in vitamin A. In animals fed on diets deficient in vitamin A the lipoid solvent remains *en masse*, whereas it disperses into small droplets where the diet is rich in vitamin A. The tissue reaction is altered in degree if the fats are removed from the solvent with ether before its injection, that is, the reaction is more rapid. Rats injected subcutaneously with certain lipoid solvents or mixtures of them and fed a diet rich in vitamin A suffer massive fatty infiltration of the liver which occurs at different time periods after the injection of different lipoid solvents. The rapid necrosis of liver produced by chloroform is due to its dissemination throughout the system, the lesion being similar to that produced locally by coal tar. The feeding of high-carbohydrate diets lessens this necrosis whereas the feeding of diets rich in vitamin A do not, although combined diets prevent necrosis more thoroughly than high-carbohydrate diets alone.

The Involvement of the Aortic Valve in Syphilitic Aortitis.—SAPHIR and SCOTT (*Am. J. Path.*, 1927, **3**, 527) present the results of studies on a series of 71 cases. Blocks were made from various parts of the ascending and descending aorta and from different parts of the aortic valve, most of which were stained with hematoxylin and eosin, others with Weigert's elastic tissue and van Gieson's connective-tissue stains. Sections from 10 cases of chronic nonsyphilitic endocarditis of aortic valves were used as controls. Uniform widening of the commissures was present, which is pathognomic of syphilis of the aortic valves. As some of the cases showed widening of the commissure without deposition of hyalin, they believe there must be some other explanation for its occurrence, namely, the adhesions formed between the lateral parts of the leaflets and the aortic intima; the deposition of hyalin plaques in this area being secondary. Histologically the most constant findings are an endarteritis obliterans of the vasa vasorum and perivascular infiltrations of lymphocytes. The earlier cases show endarteritis obliterans without perivascular lymphocytic infiltration. These changes are found more frequently and more pronounced in the adventitia. The necrosis of the media is probably secondary and attributable to nutritional disturbances resulting from this endarteritis. Histologically the affected parts of the leaflets and the aortic wall of the sinus of Valsalva show first degenerative and later inflammatory changes.

Experimental Atherosclerosis and Blood Pressure in the Rabbit.—The relation between atherosclerosis and blood pressure has been investigated by several workers following the reports of Fahr and van Leersum that rabbits fed on abnormal diets (egg, liver) develop high

blood pressure. DOMINQUEZ (*J. Exp. Med.*, 1927, **46**, 463) reports the results of feeding egg yolk to five rabbits provided with a good carotid loop by van Leersum's method. The blood pressure was measured daily before and during the egg feeding until the animal's death. The duration of the experiments varied from eighty-one to three hundred and ninety-one days and the number of egg yolks consumed from 40 to 531. Two animals received lead carbonate by mouth in addition to the egg yolk. He briefly reviews the reports of other workers and comes to the following conclusions—van Leersum's range for normal blood pressure in the rabbit, 90 to 176 mm. Hg, as recorded by his method, is confirmed. The influence of liver diet on the blood pressure is not confirmed, since the fluctuations of blood pressure recorded and ascribed to liver diet are within the range reported for normal animals. Fluctuations of systolic blood pressure beyond the "normal" range are not necessary for the production of experimental atherosclerosis of the aorta in rabbits. On the other hand, egg-yolk feeding experiments in rabbits, in which atherosclerosis of varying degrees was obtained, were not accompanied by an increase in blood pressure beyond the "normal" range. The fluctuations of blood pressure observed during the production of experimental atherosclerosis do not simulate the condition of essential hypertension in man.

Enlargement of the Adrenal Cortex in Experimental Uremia.—MACKAY and MACKAY (*J. Exp. Med.*, 1927, **46**, 429) noticed that the adrenal glands of individuals dying of uremia, in the terminal stages of Bright's disease, were larger than those found at postmortem following death from other causes. As secondary infection was usually present in these cases, a series of experiments was performed upon seventy albino rats to determine the effect of uncomplicated experimental uremia upon the adrenal glands. Only cases with retention of abnormal amounts of nonprotein nitrogen in the blood were considered uremic. This condition was produced by double nephrectomy; control rats were treated in exactly the same manner except that their kidneys were only exposed. Sixty hours later the rats were weighed, and the urea content of blood from the aorta determined. Following this they were killed, the adrenals removed, weighed and fixed in formalin. One half of the glands was dried in a vacuum oven at 70° C.; the other half was sectioned serially every 10 microns to determine changes in the volume of the cortex and medulla. The results obtained were rather striking. In both wet and dry weights the hypertrophy of the glands was marked, being 65 per cent in male rats and 47 per cent in female rats. This increase was due entirely to hypertrophy of the cortex which was in turn due largely to increased size of the cortical cells. The water and materials soluble in fat solvents were higher in uremic than control glands, but aside from this a true hypertrophy of the cortex still remained. Histologically the stainable fat had a more irregular disposition and was present in lesser amount in the adrenals from the uremic animals. This may be explained by the suggestion that there is decreased cholesterol content in glands from uremic animals while there is an increase in saturated fatty acids which do not take the fat stain Sudan III.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Epidemiology of Pneumonia.—Powell, Atwater and Felton (*Am. J. Hyg.*, 1926, **6**, 570) consider in this study the distribution of pneumococci among normal persons, the persistence of the organisms in the respiratory tract, the virulence of the organisms from various sources and the relations between the carrier state and season, age, sex and occupation. Four groups, aggregating 93 persons, in Boston were studied. It is shown that very few persons can long escape intimate contact with some form of the pneumococcus under the conditions of ordinary life. Half of the persons repeatedly examined during a period of seven months were carriers at some time of a fixed type of pneumococcus and it is therefore highly probable that practically everyone at some time during the course of the year is a carrier of one of these fixed types. Waves of increased prevalence of the fixed type carriers are described without accompanying cases of pneumonia. None of the 65 fixed type pneumococcus carriers had clinical pneumonia during the period of observation. Studies of the persistence of pneumococci in the respiratory tract of carriers shows that the fixed type organisms tend to disappear in less than thirty days. Exceptional persistence of a few strains for periods up to one hundred and twenty days was shown. The source of infection for carriers of fixed type pneumococci cannot usually be ascertained from the person's history, though it is clear that those in contact with cases of pneumonia are more likely than others to carry virulent fixed type organisms. The widespread distribution of carriers of pathogenic varieties of the pneumococcus makes the isolation of cases of pneumonia at best only partially effective in controlling this disease, for the organisms evidently are able to propagate themselves actively from carrier to carrier. In general these data serve to confirm the view that the disease pneumonia appears when there is a coincidence between infection with a pathogenic form of the pneumococcus and a lack of resistance in the same individual.

The Use of Tetraethyl Lead Gasoline in its Relation to Public Health.—Leake and his colleagues (*U. S. Pub. Health. Bull.*, 1926, **163**, 1.) carried on clinical and laboratory studies on individuals exposed to gasoline treated with tetraethyl lead and exposed to the exhaust gases of engines utilizing the mixture of gasoline and tetraethyl lead as fuel. In order to control the accuracy of the clinical and laboratory examination a number of nonexposed persons were examined, as

well as a number exposed to lead in such manner as to insure some clinical manifestation of lead intoxication. The examination was so conducted as to conceal from the examiner, clinician or laboratory worker the fact as to whether the individual being tested had been exposed to lead or was a control subject. In other words, the examination was purposely made "blind" to secure absolutely unbiased judgments. The results of these examinations showed no material clinical or laboratory evidence of harmful lead absorption among those exposed to leaded gasoline or its exhaust gases. An interesting by-product was the fact that many normal nonexposed individuals had lead in measurable amounts in their feces. In addition to the studies referred to, there was an investigation of alleged injuries from leaded gasoline. None of these could be substantiated. The studies were considered by a group of consultants who felt the following general conclusions to be justified: (1) Drivers of cars using ethyl gasoline as a fuel and in which the concentration of tetraethyl lead was not greater than 1 part to 1300 parts by volume of gasoline showed no definite signs of lead absorption after exposures approximating two years. (2) Employees of garages engaged in the handling and repairing of automobiles and employees of automobile service stations may show evidence of lead absorption and storage, as indicated by the lead content of the feces and the appearance of stippled cells in the blood. In garages and stations in which ethyl gasoline was used the amount of apparent absorption and storage was somewhat increased, but the effect was slight in comparison with that shown by workers in other industries where there was a severe lead hazard (Group E) and for the periods of exposures studied was not sufficient to produce detectable symptoms of lead poisoning. (3) In the regions in which ethyl gasoline has been used to the greatest extent as a motor fuel for a period of between two and three years no definite cases have been discovered of recognizable lead poisoning or other disease resulting from the use of ethyl gasoline.

Further Studies on the Relationship of Endemic Goiter to Certain Potential Foci of Infection.—OLESON and TAYLOR (*U. S. Pub. Health Rep.*, 1927, **42**, 606) sought to determine whether goiter bore any relation to the presence of foci of infection within the body of the goitrous individual. The studies were confined to decayed teeth and diseased tonsils, other foci of infection, such as gall bladder infection, being ignored. The study was begun in Cincinnati and the results there gave no evidence of positive correlation between infections and goiter. Subsequently the subject was investigated among children, chiefly in high schools, in Connecticut and somewhat different results. The latter studies are summarized as follows:

1. Examinations were made of the teeth and tonsils of 5797 boys and 6608 girls in twenty-eight localities in Connecticut for the purpose of determining whether there was a relationship between potential foci of infection in these particular structures and thyroid enlargement. 2. Records were made of slight and marked thyroid enlargements as well as slight and marked decay of teeth. The number of apparently normal tonsils, the absence of tonsils by operation, enlargement and cryptic degeneration, were also recorded. 3. Slight thyroid enlargements prevailed to the extent of 7 per cent among the boys and 29.4

per cent among the girls. One marked thyroid enlargement was found among the boys. Among the girls there were 91, or 1.3 per cent, of marked enlargements. 4. Sound teeth were found slightly more frequently among girls than among boys. Teeth without decay were found more frequently and consistently among the thyroid normal children of all age groups. Conversely, slight and marked decay were more common, except in one age group, among the thyroid-enlarged individuals. 5. Approximately one-third of the girls and a slightly smaller percentage of boys had had their tonsils removed by operation. Normal tonsils were more frequent among the girls. Hypertrophied tonsils and cryptic tonsils were less frequent among the girls than among the boys. 6. Normal tonsils were more frequent among thyroid normal boys and girls of all ages. With the exception of two age groups among the boys, all of the other age groups indicate a greater frequency of normal tonsils among thyroid normal individuals. 7. Absence of tonsils was noted more frequently among boys and girls with thyroid enlargement. 8. Hypertrophied tonsils were consistently though not markedly more frequent among boys and girls with thyroid enlargements. 9. Cryptic tonsils were more frequent among children with thyroid enlargements, the distinction being more clear among the girls.

The authors advance the following as a possible explanation of the difference in results secured in Cincinnati and in Connecticut: "Thyroid enlargements in Cincinnati are probably of the endemic type, being largely due to a deficiency of iodin. Consequently, the possible etiologic rôles of decayed teeth and diseased tonsils may be overshadowed to such an extent as not to be readily discernible. The thyroid enlargements which occur in Connecticut, however, are undoubtedly of the sporadic type, being produced by causes other than a deficiency of iodin. With the iodin deficiency factor largely lacking, the foci of infection come more prominently to the fore. Moreover, the extent of their detrimental influences is more apparent."

Arsphenamin-sodium Thiosulphate Treatment of Experimental Syphilis.—VOEGTLIN and DYER (*U. S. Pub. Health Rep.*, 1927, **42**, 1045) remark that they have previously shown that it is possible to sterilize rabbits by sufficient single doses of arsenicals of the arsphenamin group, but that the doses employed far exceed the largest doses used clinically. They sought to discover whether the arsphenamin treatment could be so modified as to permit more intensive treatment. They reasoned that since thiosulphate of sodium is known to be of therapeutic value in some cases of arsenical poisoning it might be used to prevent the toxic manifestations which might otherwise be expected to occur in intensive treatment. Sodium thiosulphate itself is of very low toxicity. The latter drug was given intravenously prior to the arsenical or simultaneously with it. It was found that the thiosulphate did not in any way decrease the therapeutic action of the arsenic preparation. It is suggested that the method is worthy of clinical trial, first, in cases exceptionally susceptible to arsenic dermatitis or jaundice, and, if successful, then given a further trial in intensive treatment of cases in general.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 16, 1928.

Effects of Temperature on the Rate of Swelling of Erythrocytes in Hypotonic Solutions.—M. H. JACOBS (from the Department of Physiology, University of Pennsylvania). One method of throwing light on the nature of cell permeability is by studying the temperature coefficients of the penetration of cells by various substances. Simple diffusion processes or processes in which physical diffusion is the limiting factor would be expected to show temperature coefficients for a rise of 10° C. of 1.25 or 1.30, while those of more complex nature would, as a rule, show values of Q_{10} of a different magnitude. The present investigation has to do with the temperature coefficient of the rate of intake of water from hypotonic solutions by the erythrocytes of the ox. Under properly chosen conditions the mechanism of hemolysis by water and by strongly hypotonic solutions is essentially an osmotic one, the point of hemolysis representing the attainment of a certain volume by the swelling erythrocyte. The time at which this point is reached may, therefore, with certain limitations, be used as an index of the rate of entrance of water. In the first experiments performed many irregularities were encountered. The temperature coefficient was at times found to be of the proper magnitude for a diffusion process but at other times its value departed very widely from such a figure and occasionally was even less than 1, that is, the process was more rapid at the lower than at the higher temperature. The cause of these irregularities was found to be a combination of two distinct effects of the temperature change—one on the velocity of the process as such and the other on the position of the final equilibrium approached by the system. This combination of effects became most troublesome when the theoretical point of equilibrium lay only slightly above the point of hemolysis, that is, in solutions which were just sufficiently hypotonic to cause hemolysis. By means of a simple apparatus which permits the measurement of times of hemolysis as short as four-fifths seconds it was possible to work with water alone and with very dilute solutions where changes in the position of the theoretical equilibrium produce negligible effects. Under these conditions the results obtained consistently gave temperature coefficients of the proper magnitude for a diffusion process. The average figure for water was found to be 1.3; for dilute sodium chlorid solutions, 1.28; for dilute sucrose solutions, 1.32.

Capillary Pressure in the Mesentery of the Rat and Guinea Pig.—EUGENE M. LANDIS (from the Department of Physiology, School of Medicine, University of Pennsylvania). Microinjection studies of the mesenteric circulation in the frog by the author (*Am. J. Physiol.*, 1926, **75**, 548; 1927, **82**, 217) have indicated that the passage of fluid through the capillary wall depends upon the balance between capillary pressure and the osmotic pressure of the plasma proteins, in agreement

with the hypothesis of Starling. In the mammal, however, it is known that the osmotic pressure of the plasma proteins is much higher than in the frog and it seemed advisable, therefore, to test the relationship further by determining the capillary pressure of the mammal, and to compare this value with the colloid osmotic pressure of the blood. Decerebrated rats and guinea pigs narcotized with veronal were used. The mesentery was exposed through a lateral body-wall incision, spread over a glass stage and covered with a continuous flow of well-aërated mammalian Ringer's solution at a temperature of 37° to 39° C. Micropipettes, with a diameter at the tip of 4 to 6 micra, were introduced into the arteriolar capillaries, venous capillaries and small arterioles, and the blood pressure in these situations was measured directly by the method previously described. Larger pipettes were used for determinations in arteries and veins, and in many instances aortic pressure was measured through a fine cannula. In both animals mean blood pressure in the mesenteric arteries was in the vicinity of 100 cm. water, and very slightly below the aortic level. In a series of the finest arterioles, however, average pressure was only 50.5 cm. in the rat and 76 cm. in the guinea pig. The gradient of pressure fall, as in the frog, continued throughout the capillary network. In the arteriolar extremity of a series of capillaries in the rat average pressure was 30 cm. compared to 17 cm. in the venous end. Five determinations of the osmotic pressure of the plasma proteins in rat's blood yielded figures between 22 and 26.5 cm. water. In the guinea pig articular capillary pressure was 38.5 cm. water and venous capillary pressure 18 cm. Similarly the colloid osmotic pressure in 3 animals ranged between 22 and 27.5 cm. water. In these 2 mammals, therefore, as well as in the frog there appears to be a balance between average capillary pressure and the osmotic pressure of the plasma proteins. Since the average pressure in the arteriolar end of the capillary is above the osmotic pressure of the plasma proteins, fluid is filtered from blood passing through this portion of the capillary. In the venous capillary, on the contrary, the excess of colloid osmotic pressure results in the absorption of fluid from the tissue spaces.

Glucose Tolerance in Experimental Obstructive Jaundice.—L. K. Ferguson (from the Department of Surgical Research, University of Pennsylvania, and Laboratory of Biochemistry, Philadelphia General Hospital). The fact that the administration of glucose is of particular value in the treatment of hepatic insufficiency in clinical cases led to a study of glucose metabolism in experimental jaundice. Medium-sized dogs were fed once daily on a standard diet consisting of: Casein, 5 gm.; lard, 3.5 gm.; glucose, 5 gm.; yeast, 0.1 gm.; ground beef heart, 6.5 gm.; bone ash, 0.4 gm.; salt mixture, 0.2 gm.; water, 2.5 gm.; per kilo of body weight.

Blood specimens were obtained from the jugular vein before feeding, and one, two, four and six hours after feeding. After obtaining control curves the common bile duct was sectioned between double ligatures, and the gall bladder removed. Blood specimens were removed as before at intervals after operation. The dogs lived seven to nine weeks. Blood-sugar determinations were made as soon as the blood was drawn by the Folin and Wu method. In dogs with a biliary obstruction there is a progressive decrease in sugar tolerance. The

explanation of this fact no doubt lies in the fact that there is a progressive loss of the power of glycogen synthesis as liver damage due to the biliary obstruction becomes more and more extensive. The relatively low fasting sugar values further suggests that the liver is unable to store glycogen in amounts large enough to keep the blood-sugar levels up to those ordinarily found. A typical experiment follows:

	Blood-sugar values, mg. per 100 cc.				
	Fasting.	First hour.	Second hour.	Fourth hour.	Sixth hour.
Control	87	95	86	75	82
Control	87	82	86	87	87
Cholecystectomy and Ligation of Common Bile Duct.					
Days after operation.					
8	68	112	134	66	66
30	68	150	135	75	66
50	55	210	243	166	60

Achondroplasia.—Withrow Morse and R. J. Titherington (from the Department of Physiological Chemistry, Jefferson Medical College, Philadelphia). Analyses of normal and achondroplastic femurs showed slight variations in inorganic constituents. A lower concentration of calcium was observed in the achondroplastic material (Ca, per cent normal diaphysis, 37.7; epiphysis, 38.26; achondroplastic diaphysis, 36.81; epiphysis, 36.85). It was concluded that such factors were secondary and attention was turned to the organic portions. Quantitative studies of Robison's bone esterase were made and the results gave a curve approximating ($x = y$), or more generally ($y = x \tan \phi$) where the angle ϕ is perhaps slightly greater than 45 degrees, when sodium monoglycerophosphate was used as the zymolyte. The effect of the enzyme on normally growing animals (rabbit and guinea pig) was studied and, as expected, no modification of rate of growth was observed. Attempts to produce the disease in fowls were made by injecting extracts of various gland substances (thyroid, parathormone, adrenalin, and so forth) into the eggs without positive results.

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